

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
4 September 2003 (04.09.2003)

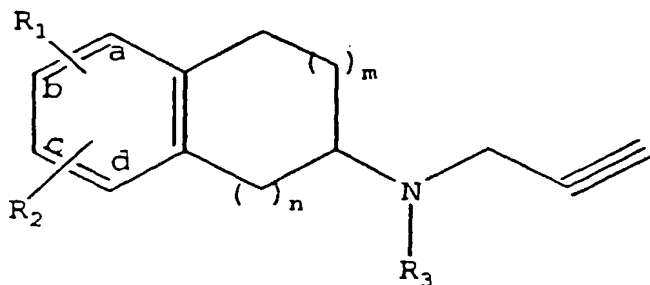
PCT

(10) International Publication Number  
**WO 03/072055 A2**

- (51) International Patent Classification<sup>7</sup>: **A61K** (74) Agent: **WHITE, John, P.**; Cooper & Dunham LLP, 1185 Avenue of the Americas, New York, NY 10036 (US).
- (21) International Application Number: PCT/US03/05871
- (22) International Filing Date: 27 February 2003 (27.02.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
10/085,674 27 February 2002 (27.02.2002) US
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- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**  
— without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Applicants: Daniella Licht et al.  
Serial No.: 10/772,911  
Filed: February 5, 2004  
**Exhibit 5**

(54) Title: PROPARGYLAMINO INDAN DERIVATIVES AND PROPARGYLAMINO TETRALIN DERIVATIVES AS BRAIN-SELECTIVE MAO INHIBITORS



(57) Abstract: The subject invention provides derivatives of propargylamino indan (PAI) and propargylamino tetralin that selectively inhibit monoamine oxidase (MAO) in the brain, having the structure: wherein R<sub>1</sub> is OC (O) R<sub>9</sub> and R<sub>2</sub> is H, wherein R<sub>9</sub> is branched or unbranched C<sub>1</sub> to C<sub>6</sub> alkyl, aryl, or aralkyl, or R<sub>1</sub> is OC (O) R<sub>4</sub> and R<sub>2</sub> is OC (O) R<sub>4</sub>, wherein R<sub>4</sub> is branched or unbranched C<sub>1</sub> to C<sub>6</sub> alkyl, aryl, aralkyl or NR<sub>5</sub>R<sub>6</sub>, wherein R<sub>5</sub> and R<sub>6</sub> are each independently H, C<sub>1</sub> to C<sub>8</sub> alkyl, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>6</sub> to C<sub>12</sub> aralkyl or C<sub>6</sub> to C<sub>12</sub> cycloalkyl, each optionally substituted; wherein R<sub>3</sub> is H or C<sub>1</sub> to C<sub>6</sub> alkyl; wherein n is 0 or 1; and wherein m is 1 or 2, or a

pharmaceutically acceptable salt thereof. Additionally, the subject invention provides methods of treating neurological disorders using these compounds, uses of these compounds for the manufacture of medicaments for treating neurological disorders and processes for synthesis of these compounds.

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PROPARGYLAMINO INDAN DERIVATIVES AND PROPARGYLAMINO  
TETRALIN DERIVATIVES AS BRAIN-SELECTIVE MAO INHIBITORS

This application claims the benefit of U.S. Serial No.  
5 10/085,674, filed February 27, 2002, the contents of which are  
hereby incorporated by reference.

Throughout this application, various references are referenced  
by short citations within parenthesis. Full citations for these  
10 references may be found at the end of the specification,  
immediately preceding the claims. These references, in their  
entireties, are hereby incorporated by reference to more fully  
describe the state of the art to which this invention pertains.

15 Field of the Invention

The subject of this invention provides for derivatives of  
propargylaminoindans and propargylaminotetralins that are  
irreversible inhibitors of the enzyme monoamine oxidase A and/or  
20 B and also for prodrugs for the administration of these  
compounds. Such compounds may be useful in the treatment of  
Parkinson's disease, Alzheimer's disease, depression and other  
neurological disorders.

25 Background of the Invention

The enzyme monoamine oxidase (MAO) plays an essential role in  
the metabolic degradation of important amine neurotransmitters  
including dopamine, serotonin and noradrenaline. Thus, agents  
30 that inhibit MAO are of potential therapeutic benefit for a  
variety of neurological disease indications, including  
Parkinson's disease, Alzheimer's disease, depression, epilepsy,  
narcolepsy, amyotrophic lateral sclerosis (ALS), etc. (Szelnai,  
I.; Bentue-Ferrer et al.; Loscher et al.; White et al.; U.S.  
35 Patent No. 5,744,500). Other diseases and conditions which have

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been associated with toxic levels of monoamine oxidase-B are memory disorders (The interaction of L-deprenyl and scopolamine on spatial learning/memory in rats), panic, post-traumatic stress disorder (PTSD), sexual dysfunction, attention deficit and hyperactivity syndrome (ADHD) (Potential applications for monoamine oxidase B inhibitors), attention deficit disorder (Kleywegt), and Tourette's syndrome (Treatment of Tourette's: Overview).

10 Many inhibitors of MAO are chiral molecules (U.S. Patent No. 5,744,500). Although one enantiomer often shows some stereoselectivity in relative potency towards MAO-A and -B, a given enantiomeric configuration is not always more selective than its isomer in discriminating between MAO-A and -B  
15 (Hazelhoff et al., Naunyn-Schmeideberg's Arch. Pharmacol.).

MAO inhibitors can also be classified as reversible inhibitors which inhibit the enzyme by a competitive mechanism or as irreversible inhibitors which are generally mechanism based  
20 (suicide inhibitors) (Dostert). For example, moclobemide is a reversible MAO-A-specific inhibitor (Fitton et al.) developed as an anti-depressant. Likewise, rasagiline (U.S. Patent No. 5,744,500) and selegiline (Chrisp et al.) are MAO-B-selective irreversible inhibitors.

25 Irreversible inhibitors have the advantage of lower, less frequent dosing since their MAO inhibition is not based directly on the drugs' pharmacokinetic behavior, but rather on the de novo regeneration of the MAO enzyme.

30 MAO also plays an essential role in the oxidative deamination of biogenic and food-derived amines, both in the central nervous system and in peripheral tissues. MAO is found in two functional isoenzyme forms, MAO-A and MAO-B, each of which shows  
35 preferential affinity for substrates and specificity toward

-3-

inhibitors. Thus, MAO-A preferentially oxidizes serotonin, noradrenaline and adrenaline, whereas MAO-B preferentially metabolizes phenylethylamine. Dopamine is a substrate for both forms of the enzyme (Szelenyi, I.).

5

N-Propargyl-(1R)-aminoindan is known to be a potent B-selective inhibitor of MAO (U.S. Patent No. 5,457,133). Various derivatives of this compound have been prepared and shown to have varying degrees of potency and selectivity for the inhibition of MAO-A and/or -B. There is no currently accepted theory explaining the effect of structure on the activity (SAR) of the various substituted propargylaminoindans.

10

The dopamine agonistic activity and MAO inhibitory properties of 7-(methyl-prop-2-ynylamino)-tetralin-2-ol and 7-(methyl-prop-2-ynylamino)-tetralin-2,3-diol have been reported (Hazelhoff et al., Eur. J. Pharmacol.). The details of the synthesis of these compounds have not been published, however.

15

6,7-di-O-benzoyl-2-aminotetralin has been reported as a prodrug of the dopaminergic agonist 6,7-di-hydroxy-2-aminotetralin (Horn et al.). However, no N-propargyl derivatives were reported and the compounds were not shown to have MAO inhibitory or neuroprotective activities.

20

25

7-(propyl-prop-2-ynylamino)-tetralin-2-ol has been reported as an intermediate in the preparation of 7-[(3-iodoallyl)-propylamino]-tetralin-2-ol. Only the latter has been pharmacologically characterized as D<sub>3</sub>-dopamine receptor ligand (Chumpradit et al.). No other N-alkyl substituents were described.

30

Florvall et al. report the preparation of amino acid-based prodrugs of amiflamine analogues. Amiflamine is a reversible MAO-A inhibitor.

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PCT International Application No. PCT/US97/24155 concerns carbamate aminoindan derivatives, including propargylamines, as inhibitors of MAO-A and MAO-B for the treatment of Alzheimer's disease and other neurological conditions. However, the compounds of PCT/US97/24155 are not selective for MAO over acetylcholinesterase ("AChE"). Thus, the compounds generally inhibit acetylcholinesterase along with MAO. Acetylcholinesterase inhibition is a route implicated in certain neurological disorders, but is a different route from the route of MAO inhibition.

U.S. Patent No. 6,303,650 discloses derivatives of 1-aminoindan as selective MAO B inhibitors that additionally inhibit acetylcholinesterase. The reference teaches that its compounds can be used to treat depression, Attention Deficit Disorder (ADC), Attention Deficit and Hyperactivity Disorder (ADHD), Tourette's Syndrome, Alzheimer's Disease and other dementias such as senile dementia, dementia of the Parkinson's type, vascular dementia and Lewy body dementia.

Many irreversible MAO inhibitors contain the propargyl amine functionality. This pharmacophore is responsible for the MAO inhibitory activity of such compounds. Some propargylamines have been shown to have neuroprotective/neurorescue properties independent of their MAO inhibition activity (U.S. Patent No. 4,844,033; Krageten et al.).

PCT International Application No. PCT/IL96/00115 relates to pharmaceutical compositions comprising racemic, (S), and (R)-N-propargyl-1-aminoindan. (R)-N-propargyl-1-aminoindan selectively inhibits MAO-B in the treatment of Parkinson's disease and other neurological disorders (PCT/IL96/00115).

Derivatives of 1-aminoindan, including propargyl aminoindan, and their salts are described in many U.S. patents (U.S. Patents No.

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5,639,913, 5,877,221, 5,880,159, 5,877,218, 5,914,349,  
5,994,408) and a PCT International Application (PCT/US95/00245).  
These references disclose racemic, R and S enantiomers of 1-  
aminoindan derivatives for the treatment of Parkinson's disease  
5 and other neurological conditions (U.S. Patents No. 5,639,913,  
5,877,221, 5,880,159, 5,877,218, 5,914,349, 5,994,408,  
PCT/US95/00245).

10 PCT International Application No. PCT/US97/24155 concerns  
aminoindan derivatives, including propargyl aminoindan, as  
inhibitors of MAO-A and MAO-B for the treatment of Parkinson's  
disease and other neurological conditions. The publication  
reveals that the disclosed compounds exhibit a greater  
selectivity for MAO-A and MAO-B in the brain than in the liver  
15 or intestine.

U.S. Patent No. 6,316,504 discloses that the R(+) enantiomer  
of N-propargyl-1-aminoindan is a selective irreversible  
inhibitor of MAO-B. The patent indicates that (R)-  
20 N-propargyl-1-aminoindan is useful for the treatment of  
Parkinson's disease, a memory disorder, dementia, depression,  
hyperactive syndrome, an affective illness, a neurodegenerative  
disease, a neurotoxic injury, stroke, brain ischemia, a head  
trauma injury, a spinal trauma injury, neurotrauma,  
25 schizophrenia, an attention deficit disorder, multiple  
sclerosis, and withdrawal symptoms.

European Patent No. 436492 discloses the R enantiomer of N-  
propargyl-1-aminoindan as a selective irreversible inhibitor of  
30 MAO-B in the treatment of Parkinson's disease and other  
neurological conditions. Numerous U.S. patents also relate to  
the MAO B inhibition of (R)-N-propargyl-1-aminoindan and its use  
for treating patients suffering from Parkinson's Disease and  
other neurological disorders (U.S. Patents No. 5,387,612,  
35 5,453,446, 5,457,133, 5,519,061, 5,532,415, 5,576,353,

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5,668,181, 5,744,500, 5,786,390 and 5,891,923).

PCT International Application No. PCT/IL97/00205 discloses S-  
(-)-N-propargyl-1-aminoindan or a pharmaceutically acceptable  
5 salt thereof for the treatment of a neurological disorder of  
neurotrauma or for improving memory. The compounds were found  
to be neuroprotective, but not inhibitory of MAO-A or MAO-B  
(PCT/IL97/00205).

10 U.S. Patent No. 5,486,541 provides N-propargyl-1-aminoindan  
monofluorinated in the phenyl ring as selective inhibitors of  
MAO-B. These compounds are presented as useful in the treatment  
of Parkinson's disease, memory disorders, dementia of the  
Alzheimer's type, depression and the hyperactive syndrome in  
15 children.

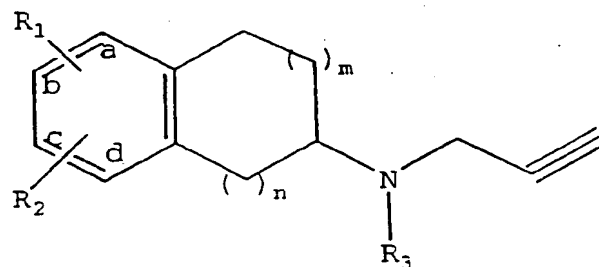
Among the many derivatives of propargylaminoindan mentioned in  
the prior art are hydroxy-propargylaminoindans. U.S. Patent No.  
3,513,244 lists some racemic N-propargylamino indanols and  
20 tetralinols for use as antihypertensives. These compounds are  
not exemplified chemically and are not pharmacologically  
characterized (U.S. Patent No. 3,513,244).

N-propargylamino indanol also appears in E.P. 267024 as a  
25 hydrofluorene derivative, i.e., 3-amino-4-indanol (7-OH  
fluorene). The hydrofluorene derivatives and salts in E.P.  
267024 are employed as cerebral activators in the treatment of  
anoxemia and hypoxemia. In addition, such derivatives help  
prevent arrhythmia and heart failure caused by lack of oxygen  
30 (E.P. 267024). The derivatives also act as antioxidants and  
cholinergic nerve system activating agents (E.P. 267024).

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Summary of the Invention

The subject invention provides a compound having the structure:



wherein  $R_1$  is  $OC(O)R_9$  and  $R_2$  is H,

wherein  $R_9$  is branched or unbranched  $C_1$  to  $C_6$  alkyl, aryl, or aralkyl, or

$R_1$  is  $OC(O)R_4$  and  $R_2$  is  $OC(O)R_4$ ,

wherein  $R_4$  is branched or unbranched  $C_1$  to  $C_6$  alkyl, aryl, aralkyl or  $NR_5R_6$ ,

wherein  $R_5$  and  $R_6$  are each independently H,  $C_1$  to  $C_8$  alkyl,  $C_6$  to  $C_{12}$  aryl,  $C_6$  to  $C_{12}$  aralkyl or  $C_6$  to  $C_{12}$  cycloalkyl, each optionally substituted;

wherein  $R_3$  is H or  $C_1$  to  $C_6$  alkyl;

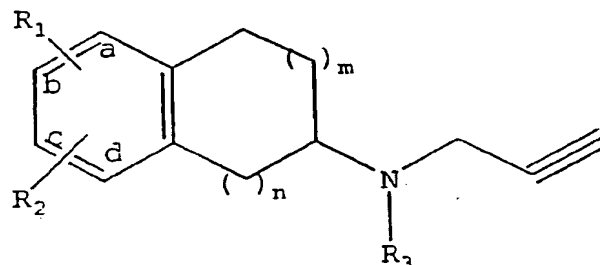
wherein  $n$  is 0 or 1; and

wherein  $m$  is 1 or 2,

or a pharmaceutically acceptable salt thereof.

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The subject invention also provides a compound having the structure:



wherein  $R_1$  is OH;

wherein  $R_2$  is H or  $OC(O)R_4$  when  $R_1$  is attached to the "a" carbon or the "d" carbon, or

$R_2$  is  $OC(O)R_4$  when  $R_1$  is attached to the "b" carbon or the "c" carbon;

wherein  $R_4$  is  $C_1$  to  $C_6$  branched or unbranched alkyl, aryl, aralkyl or  $NR_5R_6$ ,

wherein  $R_5$  and  $R_6$  are each independently H,  $C_1$  to  $C_8$  alkyl,  $C_6$  to  $C_{12}$  aryl,  $C_6$  to  $C_{12}$  aralkyl or  $C_6$  to  $C_{12}$  cycloalkyl, each optionally substituted;

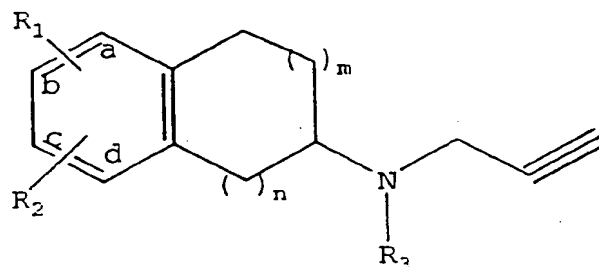
wherein  $n$  is 0 or 1, and  $m$  is 1 or 2; and

wherein  $R_3$  is H or Me when  $n$  is 1 and  $m$  is 1, or  $R_3$  is H or  $C_1$  to  $C_6$  alkyl when  $n$  is 0 or  $m$  is 2,

or a pharmaceutically acceptable salt thereof.

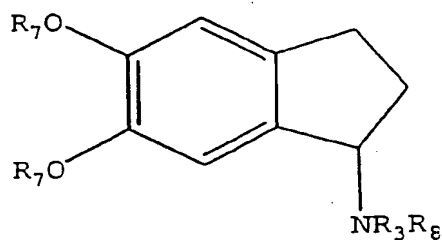
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In addition, the subject invention provides a compound having the structure:



wherein the compound is an optically pure enantiomer;  
 wherein  $R_1$  is OH;  
 wherein  $R_2$  is H;  
 wherein  $R_3$  is H or  $C_1$  to  $C_6$  alkyl;  
 wherein  $n$  is 0 or 1; and  
 wherein  $m$  is 1 or 2,  
 or a pharmaceutically acceptable salt thereof.

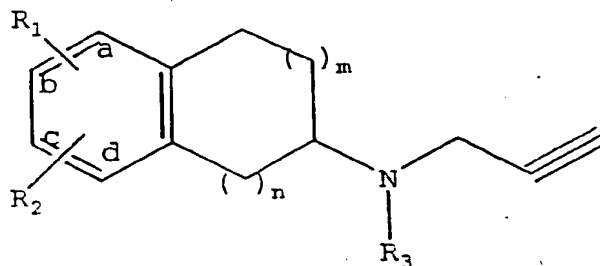
The subject invention further provides a compound having the structure:



wherein  $R_7$  is H,  $C_1$  to  $C_6$  alkyl, aryl, aralkyl or  $C(O)R_4$ ,  
 wherein  $R_4$  is branched or unbranched  $C_1$  to  $C_6$  alkyl,  
 aryl, aralkyl or  $NR_5R_6$ ,  
 wherein  $R_5$  and  $R_6$  are each independently H,  $C_1$  to  
 $C_8$  alkyl,  $C_6$  to  $C_{12}$  aryl,  $C_6$  to  $C_{12}$  aralkyl or  $C_6$  to  
 $C_{12}$  cycloalkyl, each optionally substituted;  
 wherein  $R_3$  is H or  $C_1$  to  $C_6$  alkyl;  
 wherein  $R_8$  is H or t-butoxycarbonyl (Boc).

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The subject invention also provides a method of treating a subject afflicted with a neurological disease comprising administering to the subject a compound having the structure:



wherein  $R_1$  is OH or  $OC(O)R_9$ , and wherein  $R_9$  is branched or unbranched  $C_1$  to  $C_6$  alkyl, aryl, or aralkyl;

$R_2$  is H or  $OC(O)R_4$ , or both  $R_1$  and  $R_2$  are  $OC(O)R_4$ ,

wherein  $R_4$  is branched or unbranched  $C_1$  to  $C_6$  alkyl, aryl, aralkyl or  $NR_5R_6$ ,

wherein  $R_5$  and  $R_6$  are each independently H,  $C_1$  to  $C_8$  alkyl,  $C_6$  to  $C_{12}$  aryl,  $C_6$  to  $C_{12}$  aralkyl or  $C_6$  to  $C_{12}$  cycloalkyl, each optionally substituted;

wherein  $R_3$  is H or  $C_1$  to  $C_6$  alkyl;

wherein  $n$  is 0 or 1; and

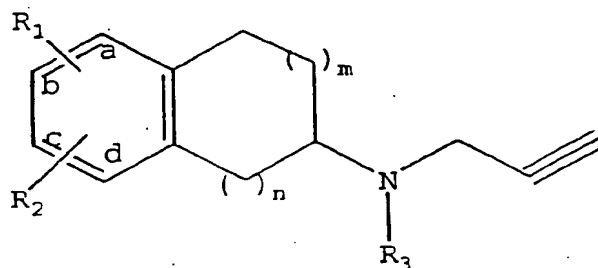
wherein  $m$  is 1 or 2,

or a pharmaceutically acceptable salt thereof, or a prodrug

which becomes the compound in the subject, so as to thereby treat the neurological disease in the subject.

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Furthermore, the subject invention provides a method of treating a subject afflicted with a neurological disease comprising administering to the subject a compound having the structure:



wherein  $R_1$  is OH or  $OC(O)R_4$ ;

wherein  $R_2$  is H or  $OC(O)R_4$ ,

15        wherein  $R_4$  is branched or unbranched  $C_1$  to  $C_6$  alkyl, aryl, aralkyl or  $NR_5R_6$ ,

          wherein  $R_5$  and  $R_6$  are each independently H,  $C_1$  to  $C_8$  alkyl,  $C_6$  to  $C_{12}$  aryl,  $C_6$  to  $C_{12}$  aralkyl or  $C_6$  to  $C_{12}$  cycloalkyl, each optionally substituted;

20        wherein  $R_3$  is H or  $C_1$  to  $C_6$  alkyl;

          wherein  $n$  is 0 or 1; and

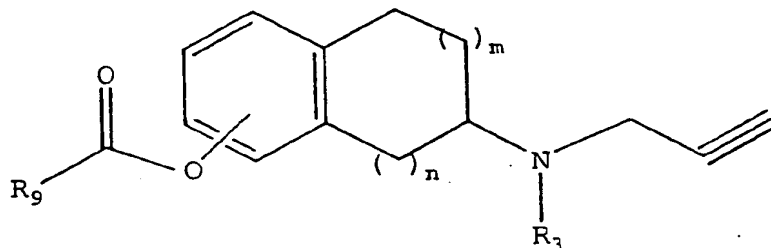
          wherein  $m$  is 1 or 2,

          or a pharmaceutically acceptable salt thereof, or a prodrug which becomes the compound in the subject, so as to thereby

25        treat the neurological disease in the subject.

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The subject invention additionally provides a process for preparing a compound having the structure:

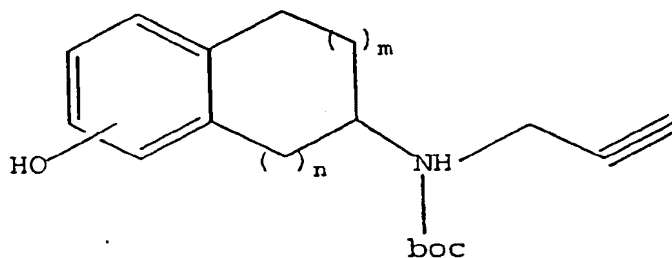


wherein  $n$  is 0 or 1, and  $m$  is 1 or 2;

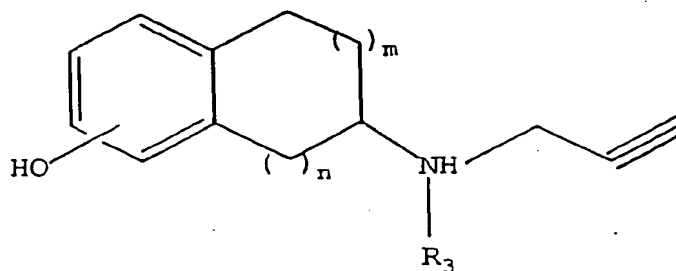
wherein  $R_3$  is H or  $C_1$  to  $C_6$  alkyl; and

wherein  $R_9$  is branched or unbranched  $C_1$  to  $C_6$  alkyl, aryl, or aralkyl;

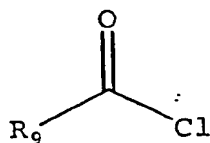
comprising the step of reacting



or



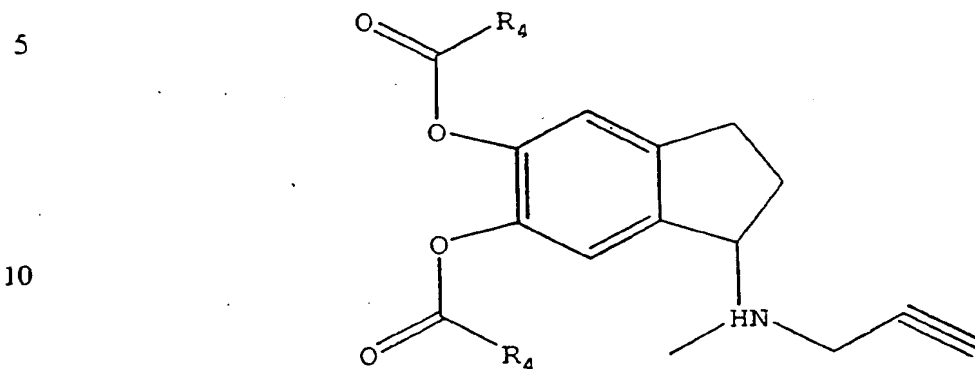
with



in the presence of an acid or 4-dimethylaminopyridine (DMAP) to form the compound.

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The subject invention also provides a process for preparing a compound having the structure:



15

wherein R<sub>4</sub> is branched or unbranched C<sub>1</sub> to C<sub>6</sub> alkyl, aryl, aralkyl or NR<sub>5</sub>R<sub>6</sub>,

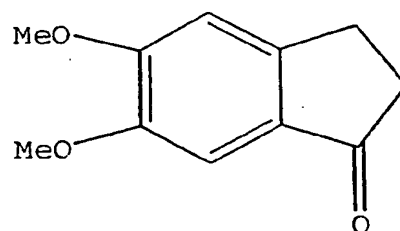
wherein R<sub>5</sub> and R<sub>6</sub> are each independently H, C<sub>1</sub> to C<sub>8</sub> alkyl, C<sub>6</sub> to C<sub>12</sub> aryl, C<sub>6</sub> to C<sub>12</sub> aralkyl or C<sub>6</sub> to C<sub>12</sub> cycloalkyl, each optionally substituted;

20

which process comprises:

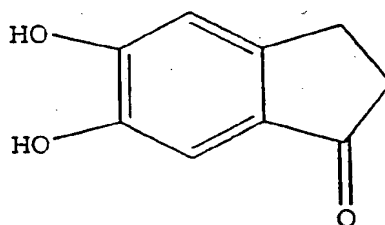
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(a) reacting a compound having the structure:



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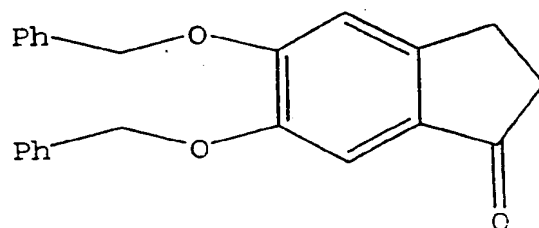
with  $\text{AlCl}_3$  or  $\text{BBr}_3$  in the presence of toluene to produce a compound having the structure:



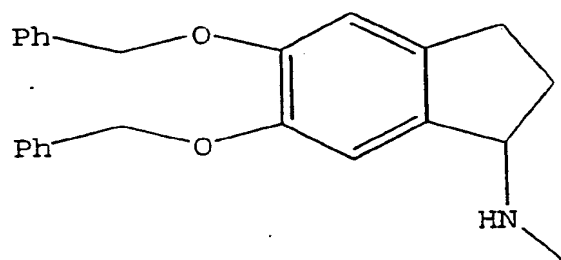
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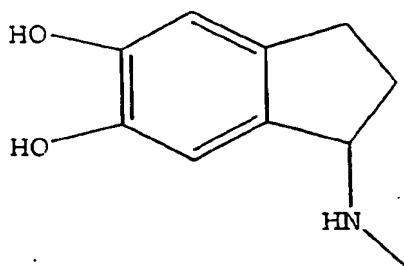
- (b) reacting the product formed in step (a) with benzyl chloride and  $K_2CO_3$  in the presence of dimethyl formamide (DMF) to produce a compound having the structure: .



- (c) reacting the product formed in step (b) with  $MeNH_2 \cdot HCl$ ,  $NaCNBH_3$  in tetrahydrofuran (THF)/MeOH to produce a compound having the structure:

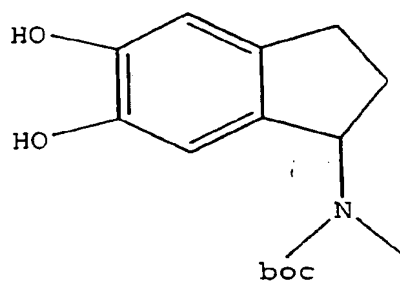


- 25 (d) reacting the product formed in step (c) with  $H_2$ , Pd/C and MeOH to produce a compound having the structure:

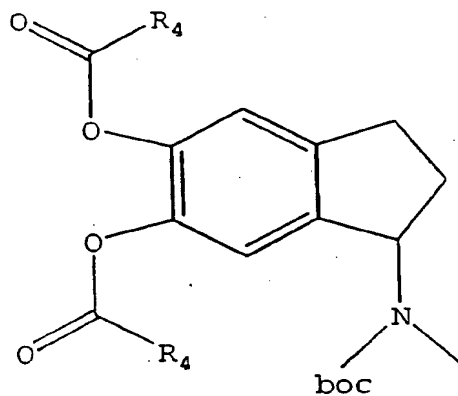


-16-

- (e) reacting the product formed in step (d) with  $\text{Boc}_2\text{O}$ , dioxane/ $\text{H}_2\text{O}$  and  $\text{NaHCO}_3$  to produce a compound having the structure:

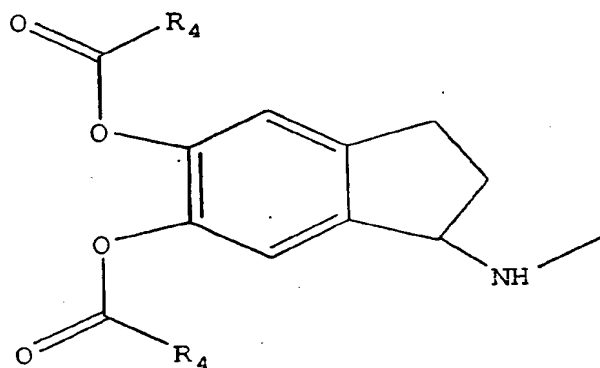


- (f) reacting the product formed in step (e) with  $\text{R}_4\text{COCl}$ ,  $\text{Et}_3\text{N}$  in  $\text{CH}_2\text{Cl}_2$  in the presence of 4-dimethylaminopyridine (DMAP) to produce a compound having the structure:

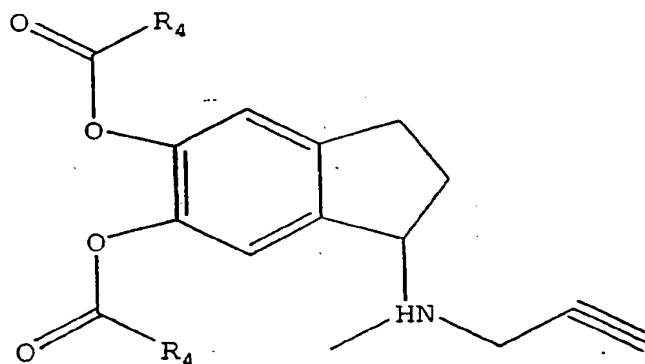


-17-

- (g) reacting the product formed in step (f) with HCl/dioxane to produce a compound having the structure:

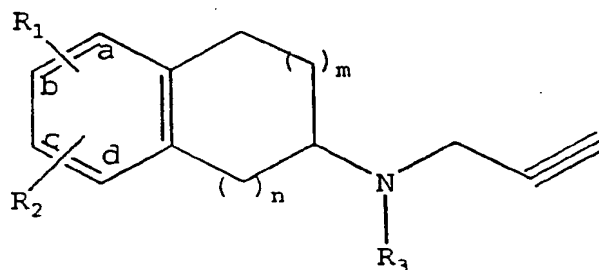


- 15 (h) reacting the product formed in step (g) with propargyl bromide, K<sub>2</sub>CO<sub>3</sub> in CH<sub>3</sub>CN and then with HCl/ether and MeOH to produce a compound having the structure:



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The subject invention also provides the use of a compound or a prodrug of a compound which becomes the compound having the structure:



wherein  $R_1$  is OH or  $OC(O)R_4$ ;

wherein  $R_2$  is H, OH or  $OC(O)R_4$ ,

wherein  $R_4$  is branched or unbranched  $C_1$  to  $C_6$  alkyl, aryl, aralkyl or  $NR_5R_6$ ,

wherein  $R_5$  and  $R_6$  are each independently H,  $C_1$  to  $C_8$  alkyl,  $C_6$  to  $C_{12}$  aryl,  $C_6$  to  $C_{12}$  aralkyl or  $C_6$  to  $C_{12}$  cycloalkyl, each optionally substituted;

wherein  $R_3$  is H or  $C_1$  to  $C_6$  alkyl;

wherein  $n$  is 0 or 1; and

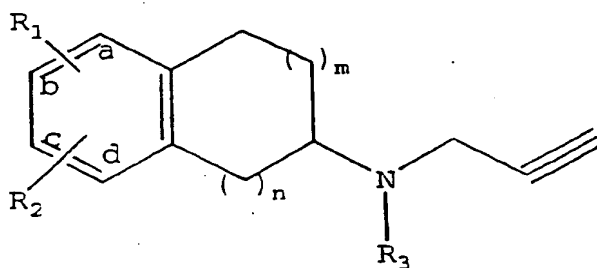
wherein  $m$  is 1 or 2,

or a pharmaceutically acceptable salt thereof,

for the manufacture of a medicament for treating a subject afflicted with a neurological disease, wherein the compound is to be periodically administered to the subject in a therapeutically effective dose.

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Additionally, the subject invention provides the use of a compound or a prodrug of a compound which becomes the compound having the structure:



wherein  $R_1$  is OH or  $OC(O)R_9$ , and

wherein  $R_9$  is branched or unbranched  $C_1$  to  $C_6$  alkyl, aryl, or aralkyl;

$R_2$  is H or  $OC(O)R_4$ , or both  $R_1$  and  $R_2$  are  $OC(O)R_4$ ,

wherein  $R_4$  is  $C_1$  to  $C_6$  alkyl, aryl, aralkyl or  $NR_5R_6$ ,

wherein  $R_5$  and  $R_6$  are each independently H,  $C_1$  to  $C_8$  alkyl,  $C_6$  to  $C_{12}$  aryl,  $C_6$  to  $C_{12}$  aralkyl or  $C_6$  to

$C_{12}$  cycloalkyl, each optionally substituted;

wherein  $R_3$  is H or  $C_1$  to  $C_6$  alkyl;

wherein  $n$  is 0 or 1; and

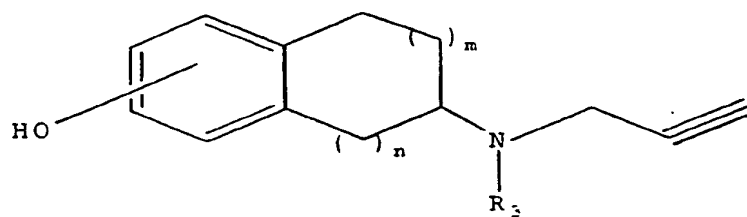
wherein  $m$  is 1 or 2,

or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating neurological disease in a subject, wherein the compound is to be periodically administered to the subject in a therapeutically effective dose.

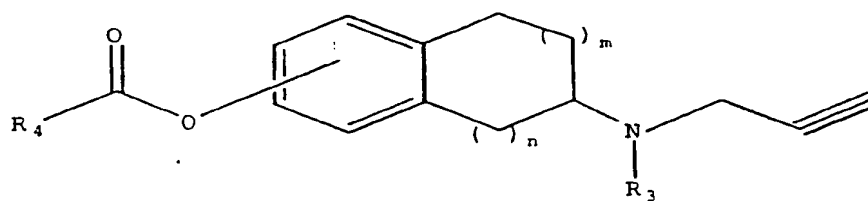
-20-

Description of the Drawings

Figure 1 presents routes for the manufacture of compounds with the following structures:

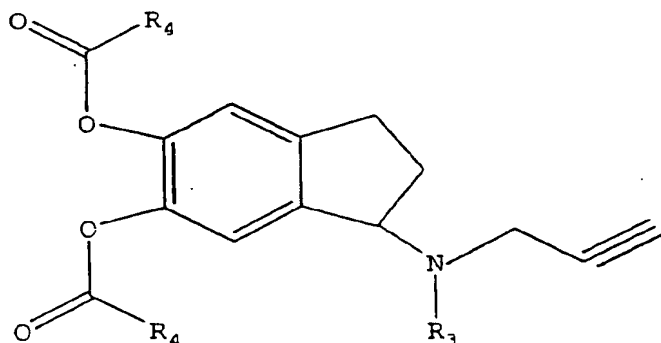


and



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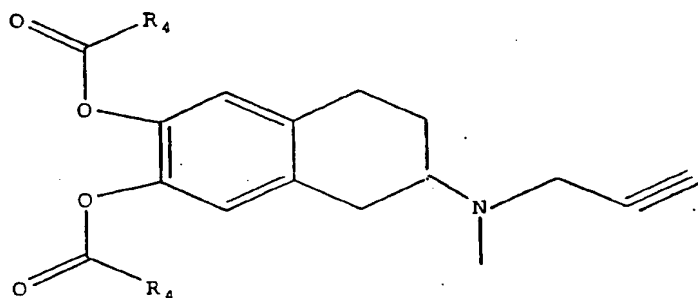
Figure 2 displays routes for the manufacture of a compound with the following structure:



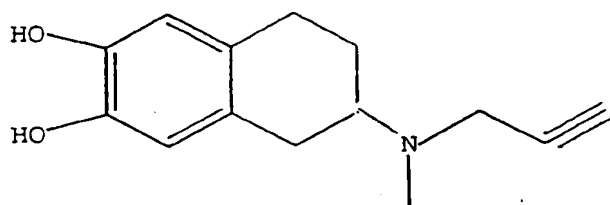
- 15 In Figure 2, the letters a) - i) are used to designate the following: a) AlCl<sub>3</sub>, toluene; b) BnCl, K<sub>2</sub>CO<sub>3</sub>, DMF; c) R<sub>3</sub>-NH<sub>2</sub>, HCl, NaCNBH<sub>3</sub>, THF/MeOH; d) H<sub>2</sub>, Pd/C, MeOH; e) Boc<sub>2</sub>O, dioxane/H<sub>2</sub>O, NaHCO<sub>3</sub>; f) R<sub>4</sub>-COCl, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>; g) HCl/dioxane; h) propargyl bromide, K<sub>2</sub>CO<sub>3</sub>, CH<sub>3</sub>CN; and i) HCl/ether, MeOH.

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Figure 3 depicts routes for the manufacture of compounds with the structures:



and

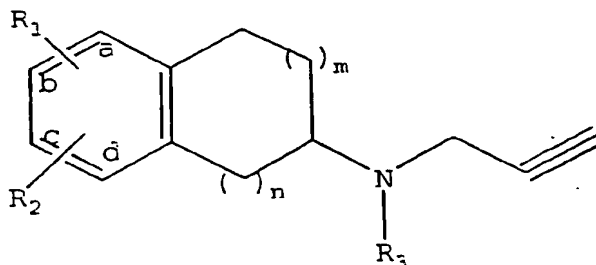


In Figure 3, the letters g) - l) are used to designate the following: g) NaCNBH<sub>3</sub>, NH<sub>4</sub>OAc; h) propargyl bromide, ACN, K<sub>2</sub>CO<sub>3</sub>; i) NaCNBH<sub>3</sub>, paraformaldehyde; j) N-methylpropargylamine, NaCNBH<sub>3</sub>; k) BBr<sub>3</sub>; and l) R<sub>4</sub>COCl, TFA or DMAP.

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Detailed Description of the Invention

The subject invention provides a compound having the structure:



wherein  $R_1$  is  $OC(O)R_2$  and  $R_2$  is H,

wherein  $R_2$  is branched or unbranched  $C_1$  to  $C_6$  alkyl, aryl, or aralkyl, or

$R_1$  is  $OC(O)R_4$  and  $R_2$  is  $OC(O)R_4$ ,

wherein  $R_4$  is branched or unbranched  $C_1$  to  $C_6$  alkyl, aryl, aralkyl or  $NR_5R_6$ ,

wherein  $R_5$  and  $R_6$  are each independently H,  $C_1$  to  $C_8$  alkyl,  $C_6$  to  $C_{12}$  aryl,  $C_6$  to  $C_{12}$  aralkyl or  $C_6$  to  $C_{12}$  cycloalkyl, each optionally substituted;

wherein  $R_3$  is H or  $C_1$  to  $C_6$  alkyl;

wherein  $n$  is 0 or 1; and

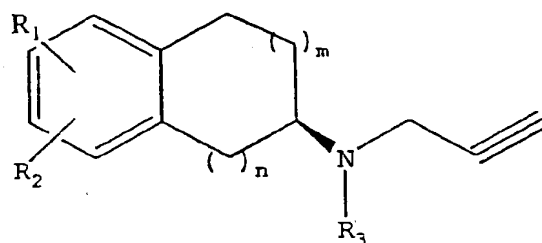
wherein  $m$  is 1 or 2,

or a pharmaceutically acceptable salt thereof.

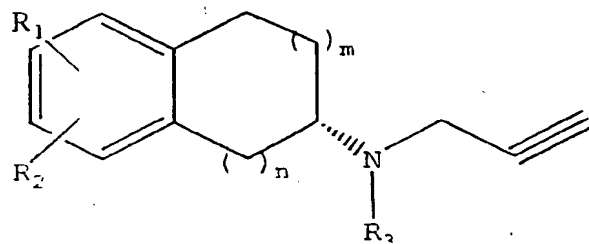
In one embodiment, the pharmaceutically acceptable salt is the acetate salt, mesylate salt, esylate, tartarate salt, hydrogen tartarate salt, benzoate salt, phenylbutyrate salt, phosphate salt, citrate salt, ascorbate salt, mandelate salt, adipate salt, octanoate salt, the myristate salt, the succinate salt, or fumarate salt.

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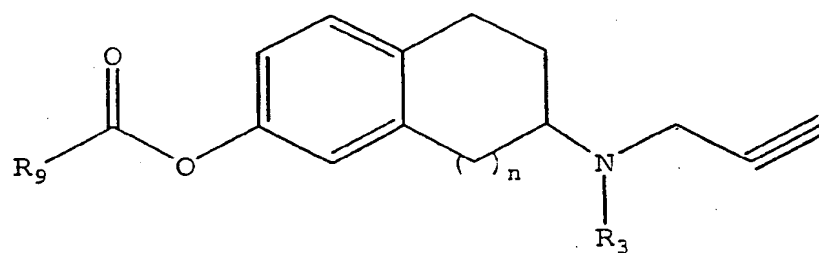
In another embodiment, the compound has the structure:



10 In a further embodiment, the compound has the structure:



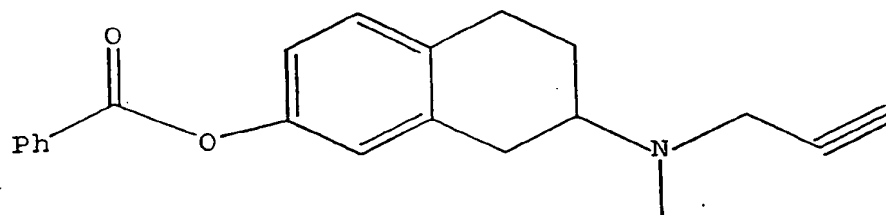
20 In yet another embodiment, the compound has the structure:



30 In one embodiment,  $n$  is 1.

-25-

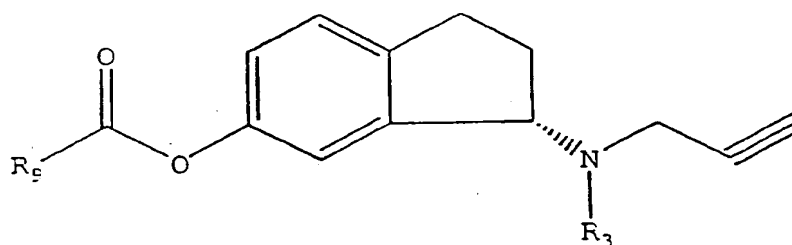
In a further embodiment, the compound has the structure:



In an added embodiment, n is 0.

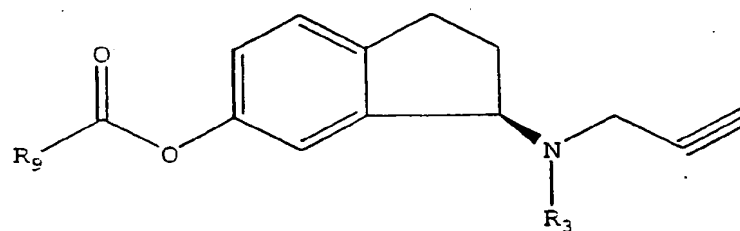
10

In yet another embodiment, the compound has the structure:



20

In still another embodiment, the compound has the structure:



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In one embodiment,  $R_9$  is Me and  $R_3$  is H.

In another embodiment,  $R_9$  is tBu and  $R_3$  is H.

In a further embodiment,  $R_9$  is nBu and  $R_3$  is H.

5

In yet another embodiment,  $R_9$  is  $\text{CH}_2\text{Ph}$  and  $R_3$  is H.

In an additional embodiment,  $R_9$  is Ph and  $R_3$  is H.

10

In still another embodiment, wherein  $R_9$  is Me and  $R_3$  is Me.

In a further embodiment,  $R_9$  is nBu and  $R_3$  is Me.

In one embodiment,  $R_9$  is Ph and  $R_3$  is Me.

15

In an added embodiment,  $R_9$  is tBu and  $R_3$  is Me.

In another embodiment,  $R_9$  is  $\text{Ph}(\text{Me})$  and  $R_3$  is Me.

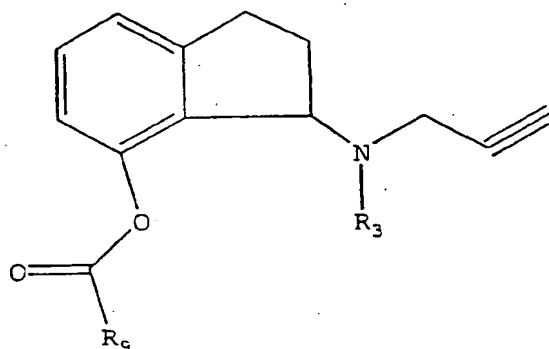
20

In still another embodiment,  $R_9$  is  $\text{Ph}(\text{OMe})_2$  and  $R_3$  is Me.

In a further embodiment,  $R_9$  is  $\text{Ph}(\text{OMe})_2$  and  $R_3$  is H.

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In one embodiment, the compound has the structure:

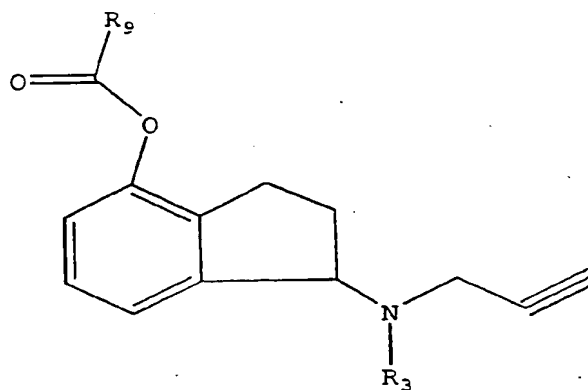


10 In an additional embodiment,  $R_3$  is Me and  $R_9$  is Me.

In a further embodiment,  $R_3$  is Me and  $R_9$  is Ph.

15 In another embodiment,  $R_3$  is Me and  $R_9$  is  $Ph(OMe)_2$ .

In yet another embodiment, the compound has the structure:



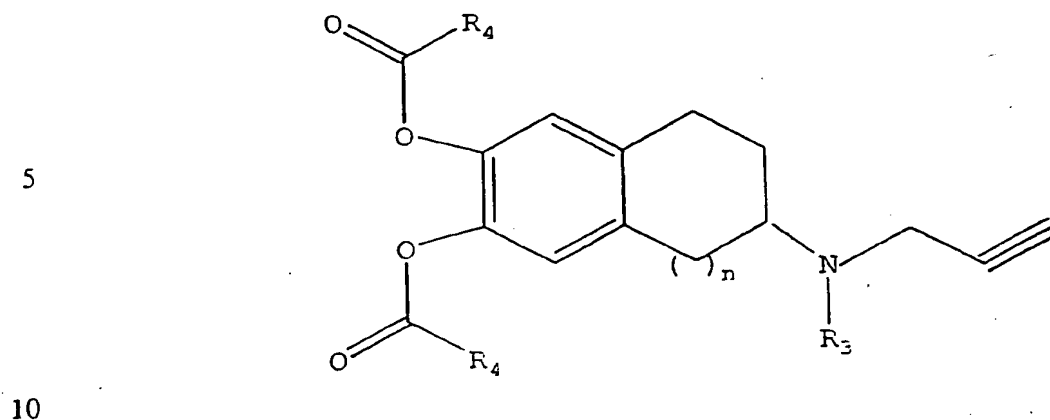
30 In an added embodiment,  $R_3$  is Me and  $R_9$  is Me.

In still another embodiment,  $R_3$  is H and  $R_9$  is Ph.

In one embodiment,  $R_3$  is H and  $R_9$  is  $Ph(OMe)_2$ .

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In another embodiment, the compound has the structure:



In a further embodiment,  $n$  is 0.

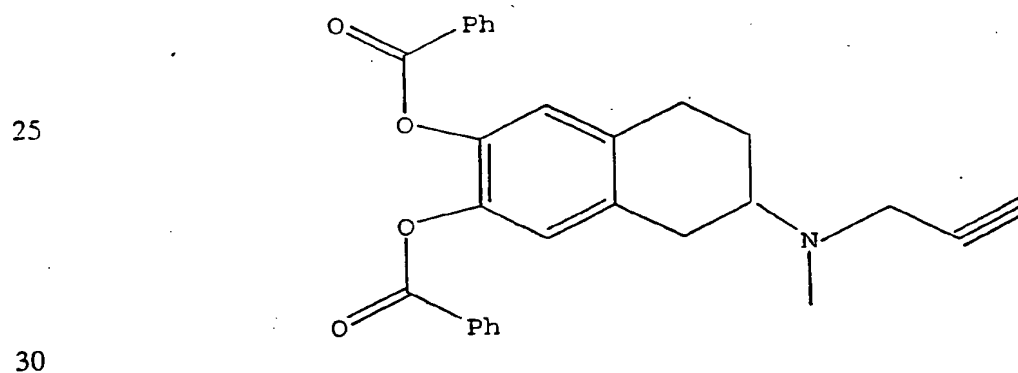
15 In yet another embodiment,  $R_4$  is Ph and  $R_3$  is Me.

In one embodiment,  $n$  is 1.

In still another embodiment,  $R_3$  is Me.

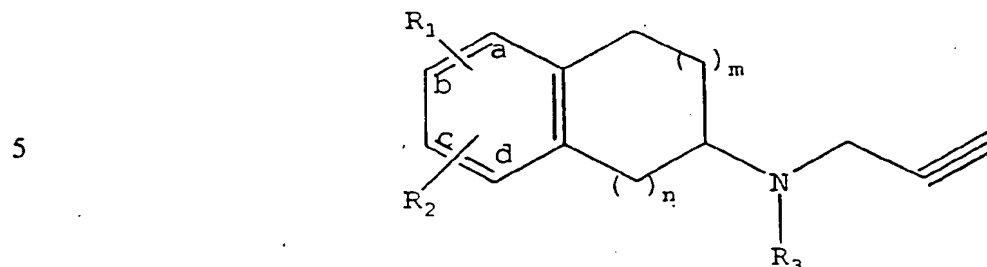
20

In an added embodiment, the compound has the structure:



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The subject invention also provides a compound having the structure:



wherein  $R_1$  is OH;

10 wherein  $R_2$  is H or  $OC(O)R_4$  when  $R_1$  is attached to the "a" carbon or the "d" carbon, or

$R_2$  is  $OC(O)R_4$  when  $R_1$  is attached to the "b" carbon or the "c" carbon;

15 wherein  $R_4$  is  $C_1$  to  $C_6$  branched or unbranched alkyl, aryl, aralkyl or  $NR_5R_6$ ,

wherein  $R_5$  and  $R_6$  are each independently H,  $C_1$  to  $C_6$  alkyl,  $C_6$  to  $C_{12}$  aryl,  $C_6$  to  $C_{12}$  aralkyl or  $C_6$  to  $C_{12}$  cycloalkyl, each optionally substituted;

wherein  $n$  is 0 or 1, and  $m$  is 1 or 2; and

20 wherein  $R_3$  is H or Me when  $n$  is 1 and  $m$  is 1, or  $R_3$  is H or  $C_1$  to  $C_6$  alkyl when  $n$  is 0 or  $m$  is 2,

or a pharmaceutically acceptable salt thereof.

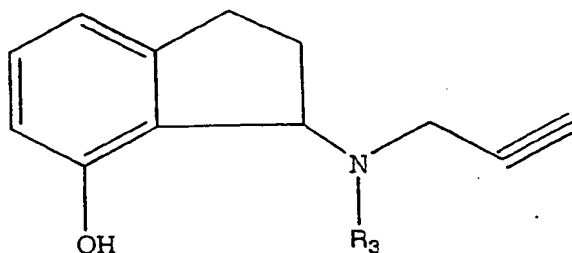
25 In one embodiment, the pharmaceutically acceptable salt is the acetate salt, mesylate salt, esylate, tartarate salt, hydrogen tartarate salt, benzoate salt, phenylbutyrate salt, phosphate salt, citrate salt, ascorbate salt, mandelate salt, adipate salt, octanoate salt, the myristate salt, the succinate salt, or fumarate salt.

30

-30-

In another embodiment, the compound has the structure:

5



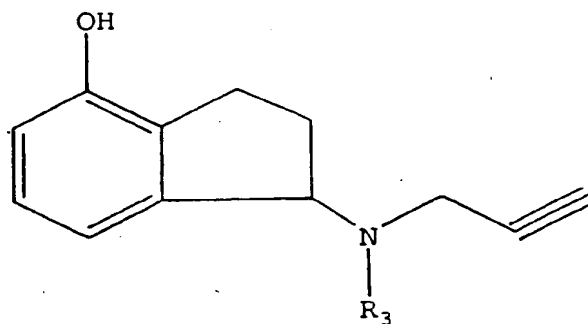
10 In an additional embodiment,  $R_3$  is H.

In a further embodiment,  $R_3$  is Me.

In yet another embodiment, the compound has the structure:

15

20



25 In still another embodiment,  $R_3$  is H.

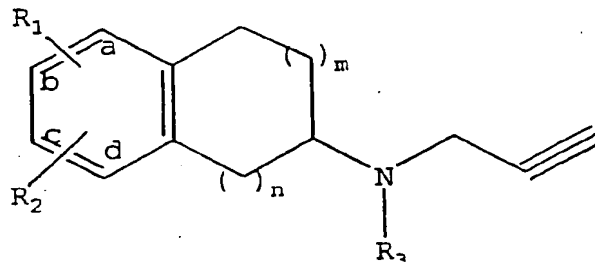
In one embodiment,  $R_3$  is Me.

In a further embodiment, n is 0.

30

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Additionally, the subject invention provides a compound having the structure:



wherein the compound is an optically pure enantiomer;

10 wherein  $R_1$  is OH;

wherein  $R_2$  is H;

wherein  $R_3$  is H or  $C_1$  to  $C_6$  alkyl;

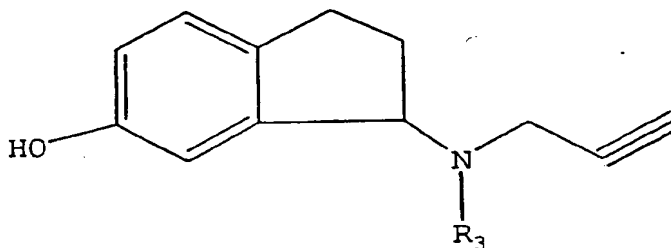
wherein  $n$  is 0 or 1; and

wherein  $m$  is 1 or 2,

15 or a pharmaceutically acceptable salt thereof.

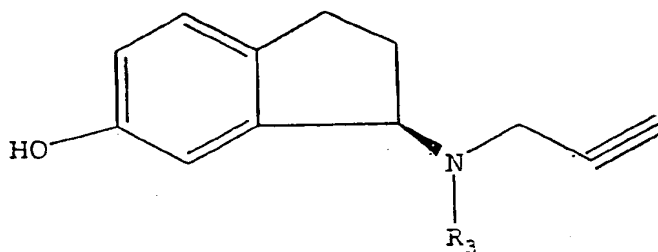
In one embodiment, the pharmaceutically acceptable salt is the acetate salt, mesylate salt, esylate, tartarate salt, hydrogen tartarate salt, benzoate salt, phenylbutyrate salt, phosphate salt, citrate salt, ascorbate salt, mandelate salt, adipate salt, octanoate salt, the myristate salt, the succinate salt, or fumarate salt.

In a further embodiment, the compound has the structure:



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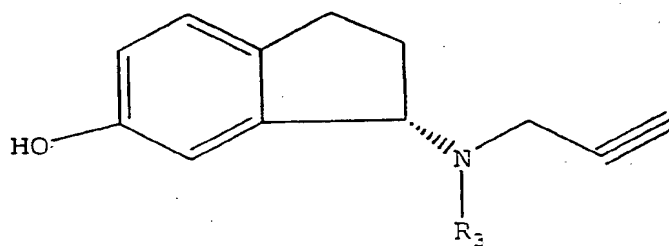
In another embodiment, the compound has the structure:



10 In an added embodiment,  $R_3$  is H.

In yet another embodiment,  $R_3$  is Me.

In a further embodiment, the compound has the structure:



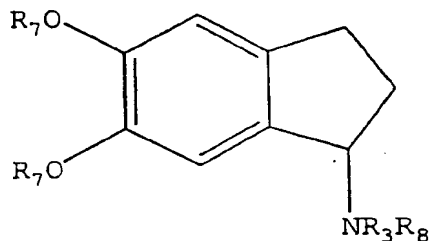
In one embodiment,  $R_3$  is H.

In another embodiment,  $R_3$  is Me.

25

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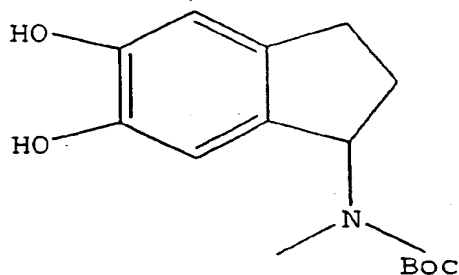
The subject invention further provides a compound having the structure:



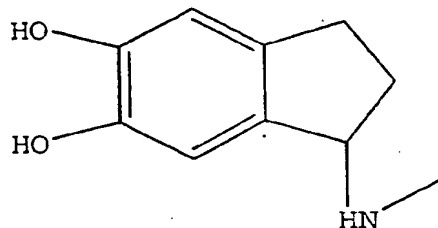
wherein  $R_7$  is H,  $C_1$  to  $C_6$  alkyl, aryl, aralkyl or  $C(O)R_4$ ,  
 wherein  $R_4$  is branched or unbranched  $C_1$  to  $C_6$  alkyl,  
 aryl, aralkyl or  $NR_5R_6$ ,

wherein  $R_5$  and  $R_6$  are each independently H,  $C_1$  to  $C_6$  alkyl,  $C_6$  to  $C_{12}$  aryl,  $C_6$  to  $C_{12}$  aralkyl or  $C_6$  to  $C_{12}$  cycloalkyl, each optionally substituted;  
 wherein  $R_3$  is H or  $C_1$  to  $C_6$  alkyl;  
 wherein  $R_8$  is H or t-butoxycarbonyl (Boc).

In one embodiment, the compound has the structure:



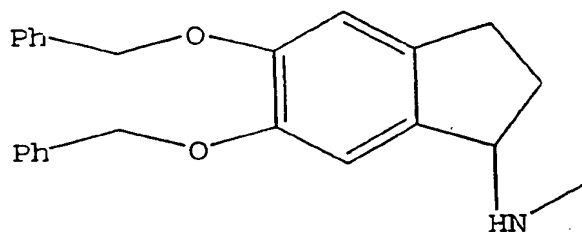
In another embodiment, the compound has the structure:



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In still another embodiment, the compound has the structure:

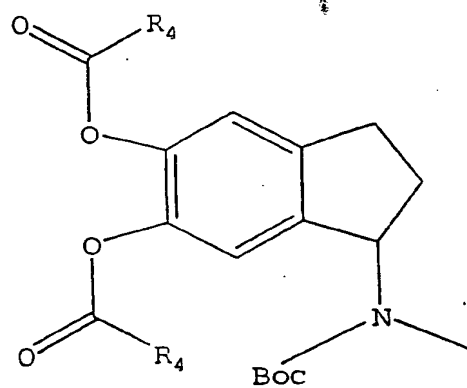
5



In an added embodiment, the compound has the structure:

10

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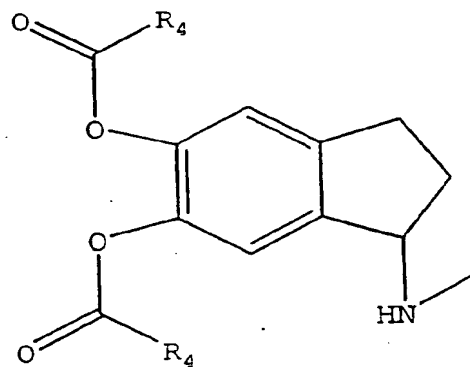
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In yet another embodiment, R<sub>4</sub> is Ph.

In one embodiment, the compound has the structure:

25

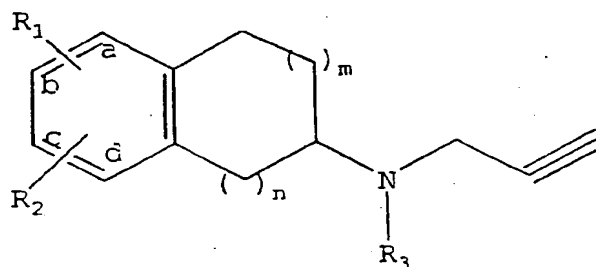
30



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In a further embodiment,  $R_4$  is Ph.

The subject invention additionally provides a pharmaceutical composition comprising a compound having the structure:



wherein  $R_1$  is  $OC(O)R_5$  and  $R_2$  is H,

wherein  $R_5$  is branched or unbranched  $C_1$  to  $C_6$  alkyl, aryl, or aralkyl, or

$R_1$  is  $OC(O)R_4$  and  $R_2$  is  $OC(O)R_4$ ,

wherein  $R_4$  is branched or unbranched  $C_1$  to  $C_6$  alkyl, aryl, aralkyl or  $NR_5R_6$ ,

wherein  $R_5$  and  $R_6$  are each independently H,  $C_1$  to  $C_8$  alkyl,  $C_6$  to  $C_{12}$  aryl,  $C_6$  to  $C_{12}$  aralkyl or  $C_6$  to  $C_{12}$  cycloalkyl, each optionally substituted;

wherein  $R_3$  is H or  $C_1$  to  $C_6$  alkyl;

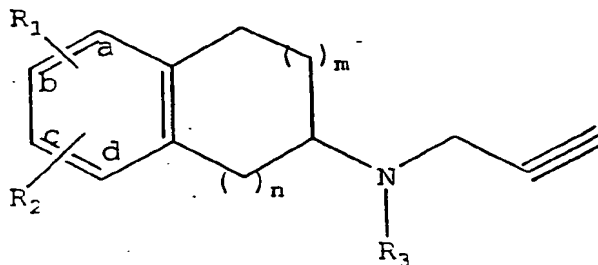
wherein  $n$  is 0 or 1; and

wherein  $m$  is 1 or 2,

or a pharmaceutically acceptable salt thereof.

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The subject invention further provides a pharmaceutical composition comprising a compound having the structure:



10 wherein  $R_1$  is OH;

wherein  $R_2$  is H or  $OC(O)R_4$  when  $R_1$  is attached to the "a" carbon or the "d" carbon, or

$R_2$  is  $OC(O)R_4$  when  $R_1$  is attached to the "b" carbon or the "c" carbon;

15 wherein  $R_4$  is  $C_1$  to  $C_6$  branched or unbranched alkyl, aryl, aralkyl or  $NR_5R_6$ ,

wherein  $R_5$  and  $R_6$  are each independently H,  $C_1$  to  $C_8$  alkyl,  $C_6$  to  $C_{12}$  aryl,  $C_6$  to  $C_{12}$  aralkyl or  $C_6$  to  $C_{12}$  cycloalkyl, each optionally substituted;

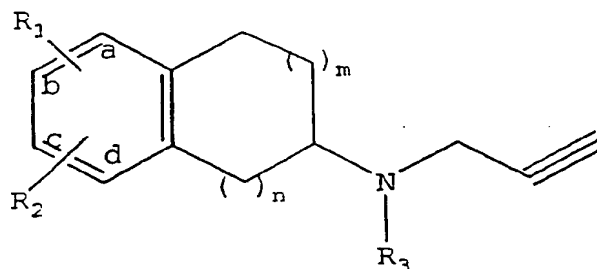
20 wherein  $n$  is 0 or 1, and  $m$  is 1 or 2; and

wherein  $R_3$  is H or Me when  $n$  is 1 and  $m$  is 1, or  $R_3$  is H or  $C_1$  to  $C_6$  alkyl when  $n$  is 0 or  $m$  is 2,

or a pharmaceutically acceptable salt thereof.

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The subject invention also provides a pharmaceutical composition comprising a compound having the structure:



10 wherein the compound is an optically pure enantiomer;

wherein  $R_1$  is OH;

wherein  $R_2$  is H;

wherein  $R_3$  is H or  $C_1$  to  $C_6$  alkyl;

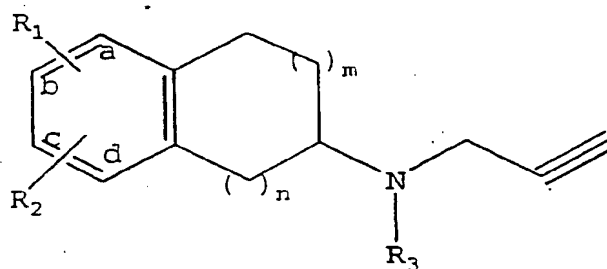
wherein  $n$  is 0 or 1; and

15 wherein  $m$  is 1 or 2,

or a pharmaceutically acceptable salt thereof.

The subject invention also provides a method of treating a subject afflicted with a neurological disease comprising administering to the subject a compound having the structure:

20



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wherein  $R_1$  is OH or  $OC(O)R_4$ ;

wherein  $R_2$  is H, OH or  $OC(O)R_4$ ,

wherein  $R_4$  is branched or unbranched  $C_1$  to  $C_6$  alkyl, aryl, aralkyl or  $NR_5R_6$ ,

wherein  $R_5$  and  $R_6$  are each independently H,  $C_1$  to  $C_8$  alkyl,  $C_6$  to  $C_{12}$  aryl,  $C_6$  to  $C_{12}$  aralkyl or  $C_6$  to  $C_{12}$  cycloalkyl, each optionally substituted;

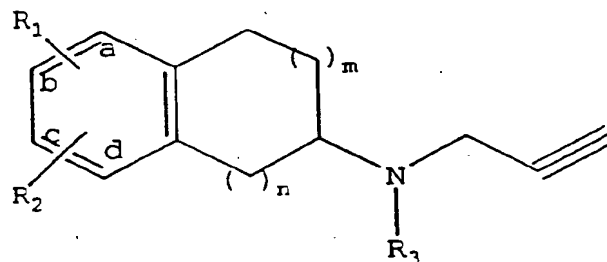
wherein  $R_3$  is H or  $C_1$  to  $C_6$  alkyl;

wherein  $n$  is 0 or 1; and

wherein  $m$  is 1 or 2,

or a pharmaceutically acceptable salt thereof, or a prodrug which becomes the compound in the subject, so as to thereby treat the neurological disease in the subject.

Additionally, the subject invention provides a method of treating a subject afflicted with a neurological disease comprising administering to the subject a compound having the structure:



wherein  $R_1$  is OH or  $OC(O)R_9$ , and  $R_2$  is H or  $OC(O)R_4$ , or both  $R_1$  and  $R_2$  are  $OC(O)R_4$ ,

wherein  $R_9$  is branched or unbranched  $C_1$  to  $C_6$  alkyl, aryl, or aralkyl;

wherein  $R_4$  is branched or unbranched  $C_1$  to  $C_6$  alkyl, aryl, aralkyl or  $NR_5R_6$ ,

wherein  $R_5$  and  $R_6$  are each independently H,  $C_1$  to  $C_8$  alkyl,  $C_6$  to  $C_{12}$  aryl,  $C_6$  to  $C_{12}$  aralkyl or  $C_6$  to  $C_{12}$  cycloalkyl, each optionally substituted;

wherein  $R_3$  is H or  $C_1$  to  $C_6$  alkyl;

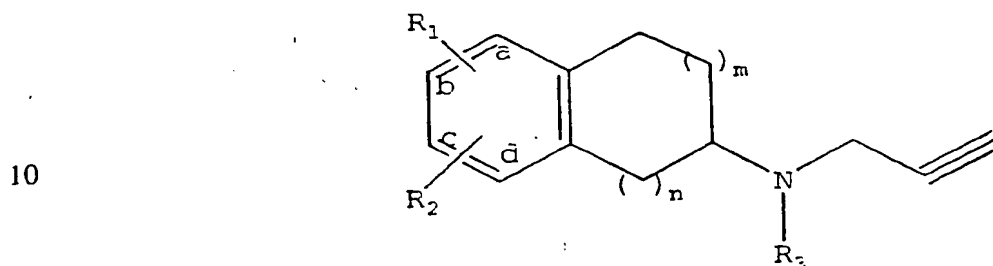
wherein  $n$  is 0 or 1; and

-39-

wherein  $m$  is 1 or 2,

or a pharmaceutically acceptable salt thereof, or a prodrug which becomes the compound in the subject, so as to thereby treat the neurological disease in the subject.

5 In one embodiment of the method, the compound has the structure:



wherein  $R_1$  is  $OC(O)R_2$  and  $R_2$  is H,

15 wherein  $R_2$  is branched or unbranched  $C_1$  to  $C_6$  alkyl, aryl, or aralkyl, or

$R_1$  is  $OC(O)R_4$  and  $R_2$  is  $OC(O)R_4$ ,

wherein  $R_4$  is branched or unbranched  $C_1$  to  $C_6$  alkyl, aryl, aralkyl or  $NR_5R_6$ ,

20 wherein  $R_5$  and  $R_6$  are each independently H,  $C_1$  to  $C_8$  alkyl,  $C_6$  to  $C_{12}$  aryl,  $C_6$  to  $C_{12}$  aralkyl or  $C_6$  to  $C_{12}$  cycloalkyl, each optionally substituted;

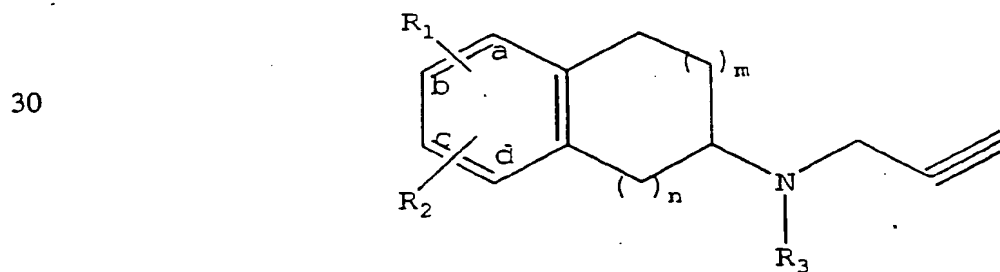
wherein  $R_3$  is H or  $C_1$  to  $C_6$  alkyl;

wherein  $n$  is 0 or 1; and

wherein  $m$  is 1 or 2.

25

In another embodiment of the method, the compound has the structure:



-40-

wherein  $R_1$  is OH;

wherein  $R_2$  is H or  $OC(O)R_4$  when  $R_1$  is attached to the "a" carbon or the "d" carbon, or

$R_2$  is  $OC(O)R_4$  when  $R_1$  is attached to the "b" carbon or the "c" carbon;

wherein  $R_4$  is  $C_1$  to  $C_6$  branched or unbranched alkyl, aryl, aralkyl or  $NR_5R_6$ ,

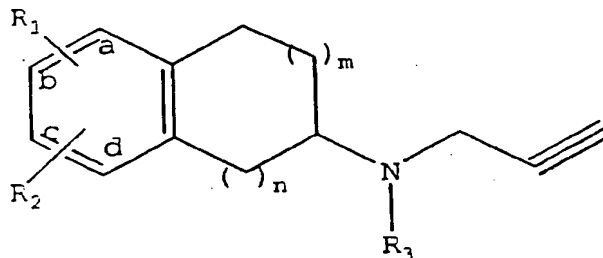
wherein  $R_5$  and  $R_6$  are each independently H,  $C_1$  to  $C_8$  alkyl,  $C_6$  to  $C_{12}$  aryl,  $C_6$  to  $C_{12}$  aralkyl or  $C_6$  to  $C_{12}$  cycloalkyl, each optionally substituted;

wherein  $R_3$  is H or  $C_1$  to  $C_6$  alkyl;

wherein  $n$  is 0 or 1; and

wherein  $m$  is 1 or 2.

In a further embodiment of the method, the compound has the structure:



wherein the compound is an optically pure enantiomer;

wherein  $R_1$  is OH;

wherein  $R_2$  is H;

wherein  $R_3$  is H or  $C_1$  to  $C_6$  alkyl;

wherein  $n$  is 0 or 1; and

wherein  $m$  is 1 or 2.

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In one embodiment, the subject is human.

In a further embodiment, the administration comprises oral, parenteral, intravenous, transdermal, or rectal administration.

5 In one embodiment, the effective amount is from about 0.01 mg per day to about 100.0 mg per day.

In yet another embodiment, the effective amount is from about 0.01 mg per day to about 50.0 mg per day.

10

In still another embodiment, the effective amount is from about 0.1 mg per day to about 100.0 mg per day.

15 In an added embodiment, the effective amount is from about 0.1 mg per day to about 10.0 mg per day.

In yet another embodiment, the effective amount is from about 0.01 mg to about 100.0 mg.

20 In one embodiment, the effective amount is from about 0.01 mg to about 50.0 mg.

In a further embodiment, the effective amount is from about 0.1 mg to about 100.0 mg.

25

In another embodiment, the effective amount is from about 0.1 mg to about 10.0 mg.

30 In an additional embodiment, the neurological disease is Parkinson's disease, Alzheimer's disease, depression, epilepsy, narcolepsy, amyotrophic lateral sclerosis (ALS), memory disorders, panic, post-traumatic stress disorder (PTSD), sexual dysfunction, attention deficit and hyperactivity syndrome (ADHD), attention deficit disorder, or Tourette's syndrome. The

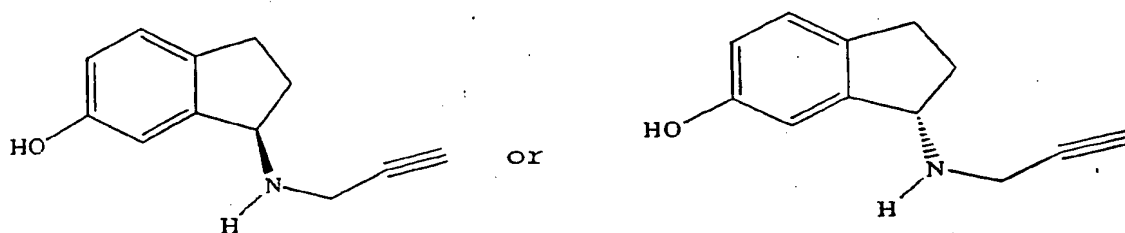
-42-

disease may also be neuropathy, hyperactive syndrome, neurotrauma, stroke, Parkinson's disease, Huntington's disease, and other dementia such as senile dementia, dementia of the vascular dementia or Lewy body dementia.

- 5 In still another embodiment, the neurological disease is depression.

In still another embodiment, the compound has the structure:

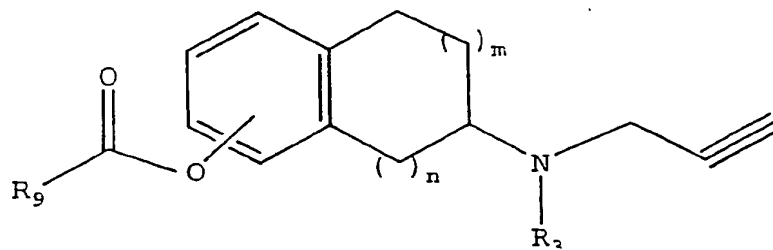
10



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The subject invention further provides a process for preparing a compound having the structure:

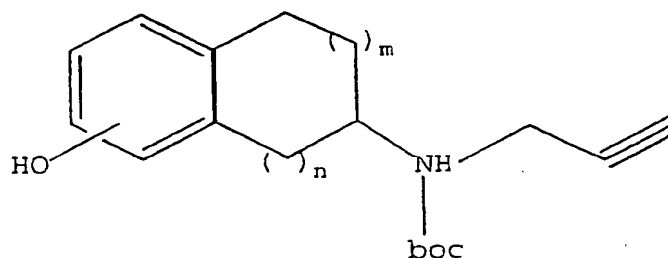


wherein  $n$  is 0 or 1, and  $m$  is 1 or 2;

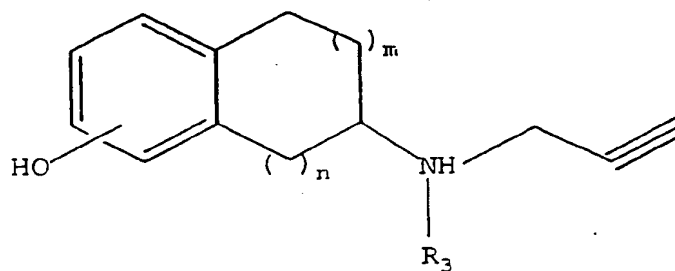
wherein  $R_3$  is H or  $C_1$  to  $C_6$  alkyl; and

10 wherein  $R_9$  is branched or unbranched  $C_1$  to  $C_6$  alkyl, aryl, or aralkyl;

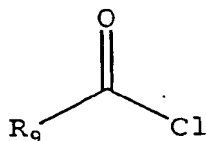
comprising the step of reacting



or



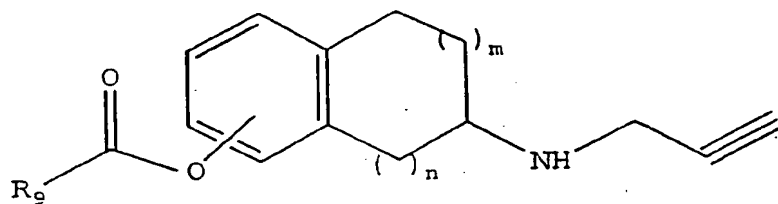
with



30 in the presence of an acid or 4-dimethylaminopyridine (DMAP) to form the compound.

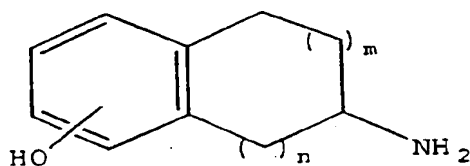
-44-

The subject invention also provides a process for preparing a compound having the structure:



wherein  $\text{R}_9$  is branched or unbranched  $\text{C}_1$  to  $\text{C}_6$  alkyl, aryl,  
10 or aralkyl;  
which process comprises:

(a) reacting a compound having the structure:

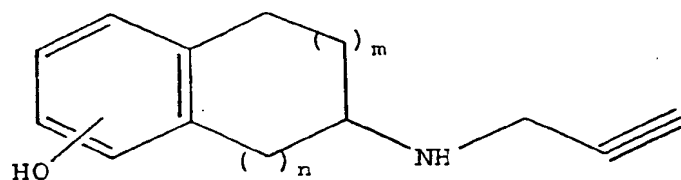


-45-

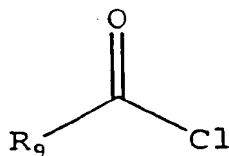
with a compound having the structure:



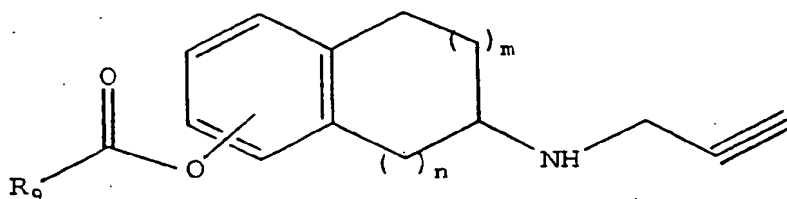
wherein X is a leaving group,  
to produce a compound having the structure:



(b) reacting the compound formed in step (a) with a compound  
having the structure:



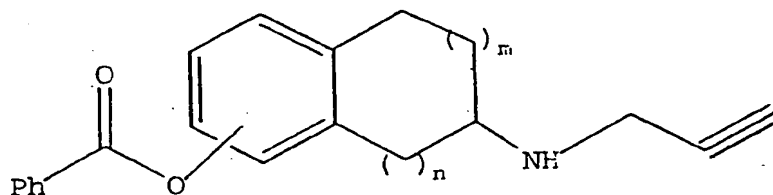
in the presence of trifluoroacetic acid (TFA) and an  
aprotic solvent to produce a compound having the structure:



In one embodiment, the leaving group in step (a) is selected  
from the group consisting of a halogen and benzene sulfonate and  
the aprotic solvent in step (b) is  $\text{CHCl}_3$ .

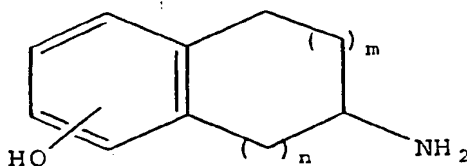
-46-

The subject invention further provides a process for preparing a compound having the structure:

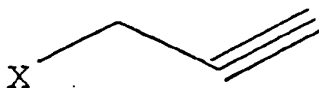


which comprises:

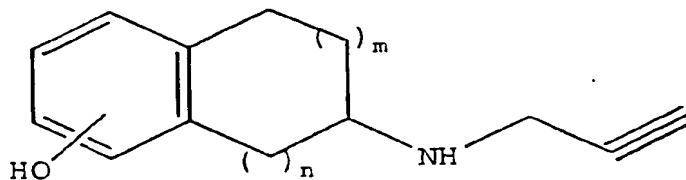
- 10 (a) reacting a compound having the structure:



with a compound having the structure:

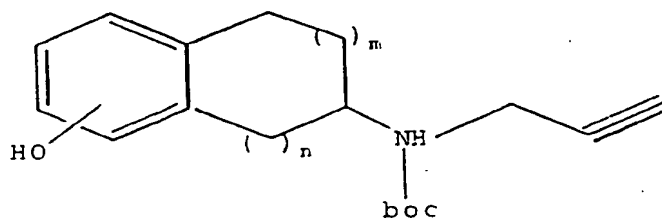


wherein X is a leaving group,  
to produce a compound having the structure:



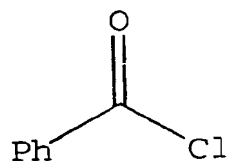
- 30 (b) N-protecting the compound formed in step (a) with tert-butoxycarbonyl (Boc) to produce a compound having the structure:

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5

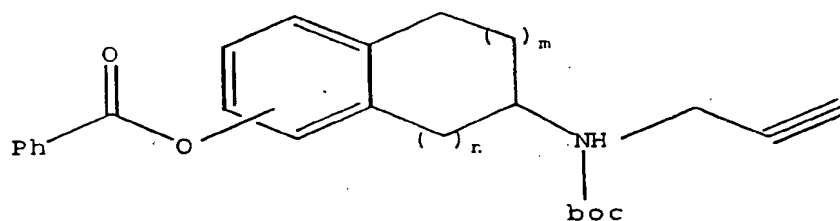
(c) reacting the compound formed in step (b) with a compound having the structure:



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in the presence of 4-dimethylaminopyridine (DMAP) to produce a compound having the structure:

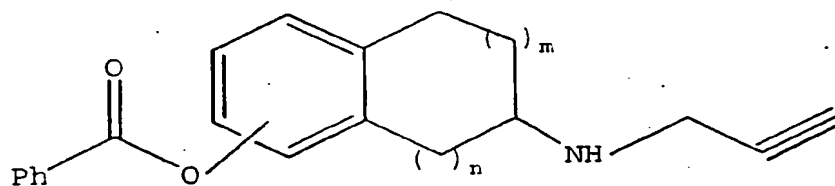
15



20

(d) deprotecting the compound formed in step (c) with HCl to produce a compound having the structure:

25



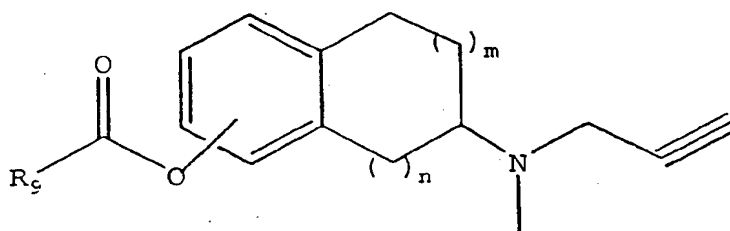
30

In one embodiment, the leaving group in step (a) is selected from the group consisting of a halogen and benzene sulfonate and the aprotic solvent in step (b) is  $\text{CHCl}_3$ .

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The subject invention additionally provides a process for preparing a compound having the structure:

5

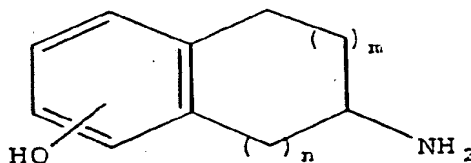


10

wherein  $R_5$  is branched or unbranched  $C_1$  to  $C_6$  alkyl, aryl, or aralkyl;  
which process comprises:

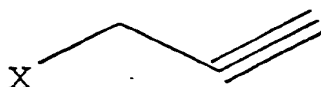
(a) reacting a compound having the structure:

15



20

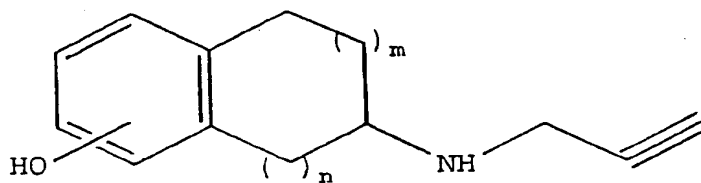
with a compound having the structure:



25

wherein X is a leaving group,  
to produce a compound having the structure:

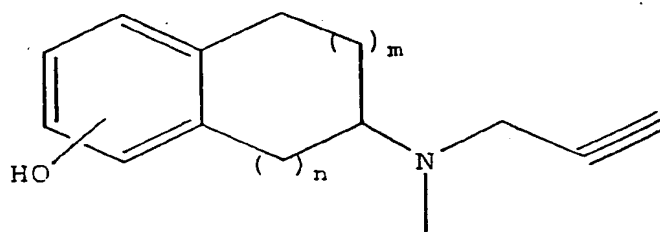
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5

- (b) reacting the compound formed in step (a) with  $\text{NaCNBH}_3$  and paraformaldehyde to produce a compound having the structure:

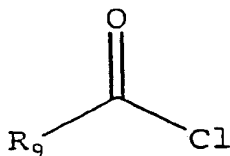
10



15

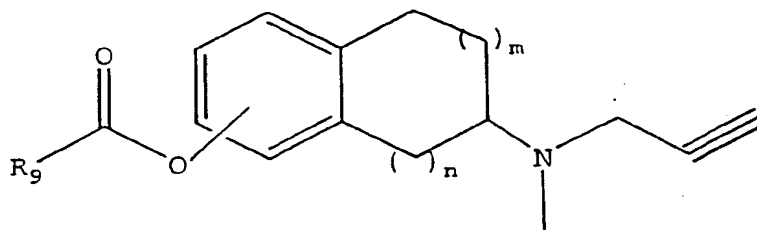
- (c) reacting the compound formed in step (b) with a compound having the structure:

20



in the presence of trifluoroacetic acid (TFA) and an aprotic solvent to form a compound having the structure:

25

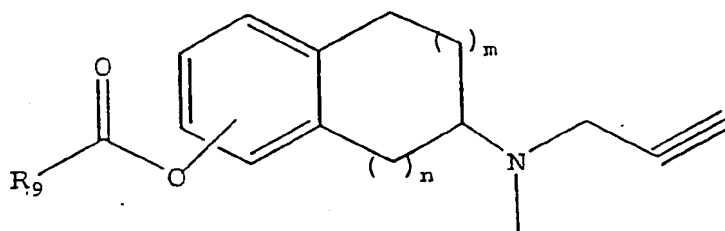


30

In one embodiment, the leaving group in step (a) is selected from the group consisting of a halogen and benzene sulfonate and the aprotic solvent in step (c) is  $\text{CHCl}_3$ .

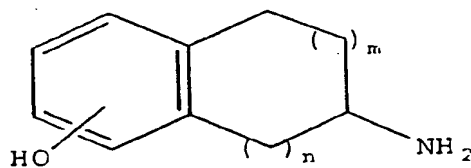
-50-

The subject invention provides another process for preparing a compound having the structure:



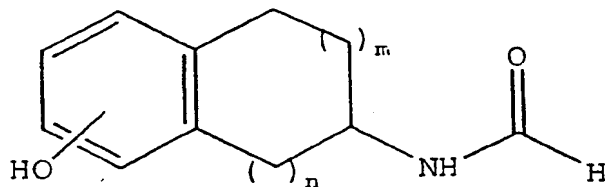
10 wherein  $\text{R}_9$  is branched or unbranched  $\text{C}_1$  to  $\text{C}_6$  alkyl, aryl, or aralkyl;  
which process comprises:

(a) reacting a compound having the structure:

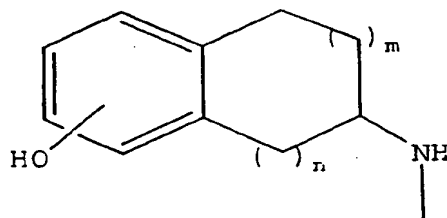


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with ethyl formate to produce a compound having the structure:

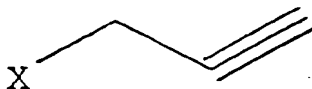


(b) reacting the compound formed in step (a) with lithium aluminum hydride to produce a compound having the structure:

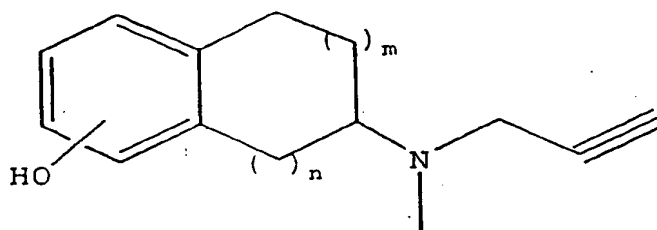


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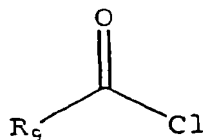
- (c) reacting the compound formed in step (b) with a compound having the structure:



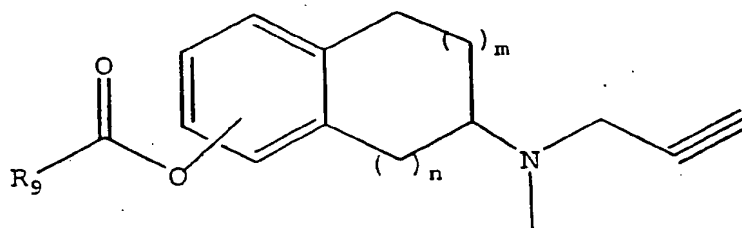
- wherein X is a leaving group,  
to form a compound having the structure:



- (d) reacting the compound formed in step (c) with a compound having the structure:



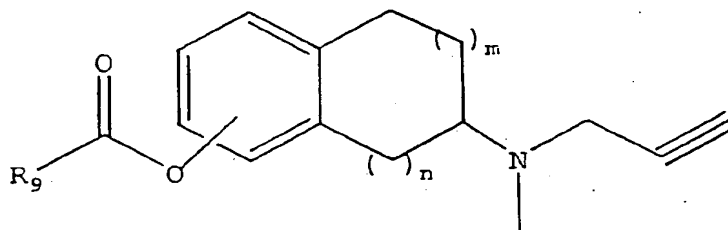
- in the presence of trifluoroacetic acid (TFA) and an aprotic solvent to form a compound having the structure:



In one embodiment, the aprotic solvent in step (c) is CHCl<sub>3</sub>.

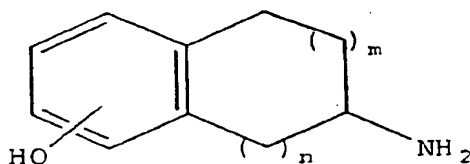
-53-

The subject invention provides yet another process for preparing a compound having the structure:



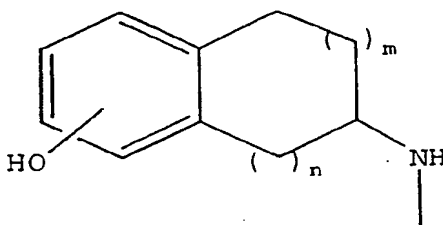
wherein  $R_9$  is branched or unbranched  $C_1$  to  $C_6$  alkyl, aryl, or aralkyl;  
which process comprises:

(a) reacting a compound having the structure:

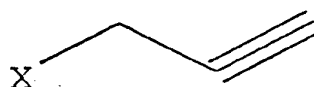


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with  $\text{NaCNBH}_3$ /paraformaldehyde to produce a compound having the structure:

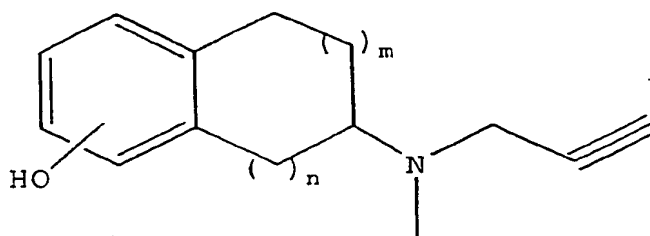


(b) reacting the compound formed in step (a) with a compound having the structure:

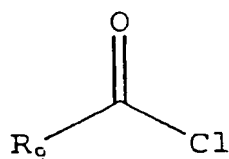


wherein X is a leaving group,  
15 to form a compound having the structure:

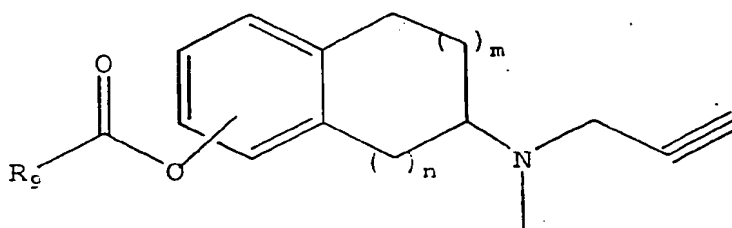
-55-



(c) reacting the compound formed in step (b) with a compound having the structure:



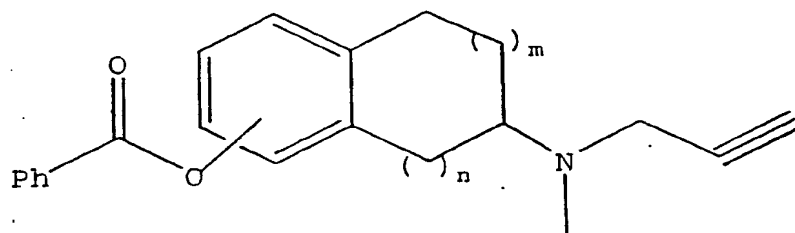
15 in the presence of trifluoroacetic acid (TFA) and an aprotic solvent to form a compound having the structure:



25 In one embodiment, the aprotic solvent in step (d) is  $\text{CHCl}_3$ .

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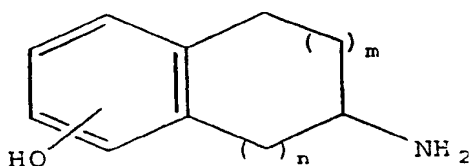
Additionally, the subject invention provides a process for preparing a compound having the structure:



which comprises:

10

(a) reacting a compound having the structure:



with a compound having the structure:

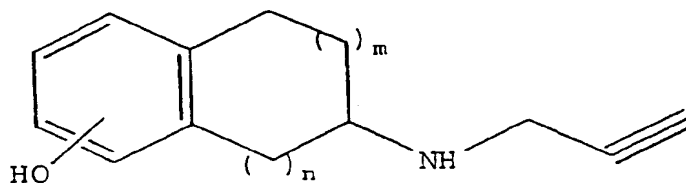
20



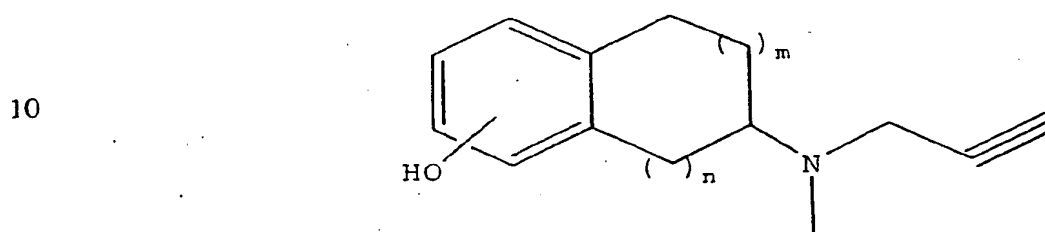
wherein X is a leaving group,

to produce a compound having the structure:

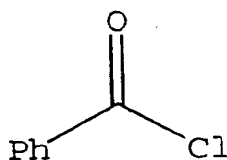
-57-



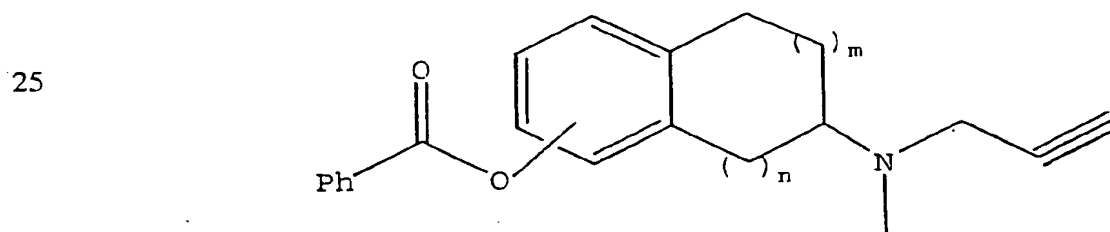
- 5 (b) reacting the compound formed in step (a) with NaCNBH<sub>3</sub> and paraformaldehyde to produce a compound having the structure:



- 10 (c) reacting the compound formed in step (b) with a compound having the structure:



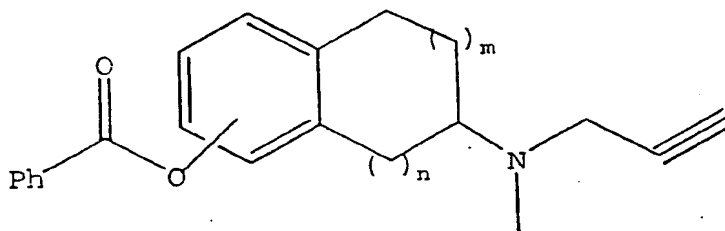
- 15 in the presence of 4-dimethylaminopyridine (DMAP) and an aprotic solvent to form a compound having the structure:



- 20 In one embodiment, the leaving group in step (a) is selected from the group consisting of a halogen and benzene sulfonate and the aprotic solvent in step (c) is CHCl<sub>3</sub>.

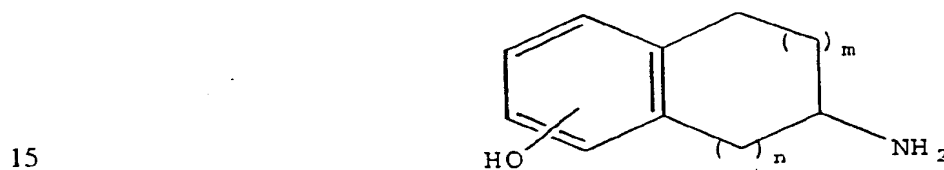
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The subject invention provides another process for preparing a compound having the structure:

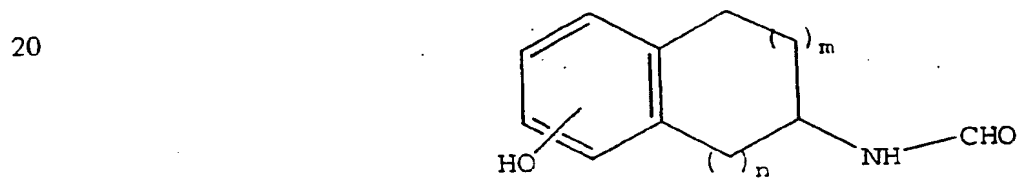


which comprises:

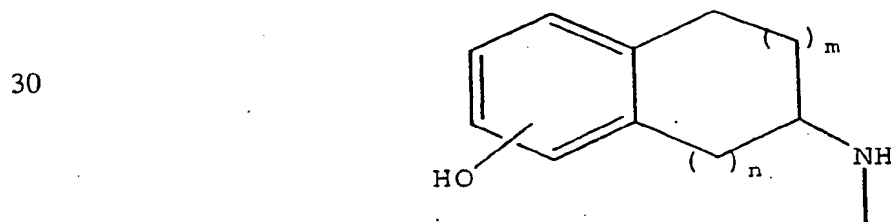
10 (a) reacting a compound having the structure:



with ethyl formate to produce a compound having the structure:



25 (b) reacting the compound formed in step (a) with lithium aluminum hydride to produce a compound having the structure:

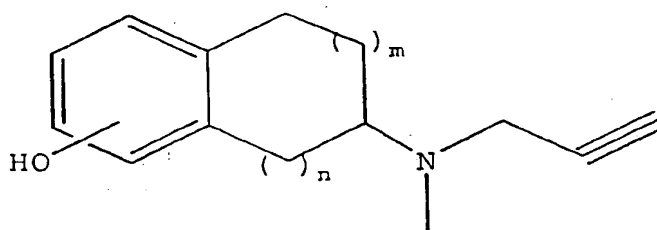


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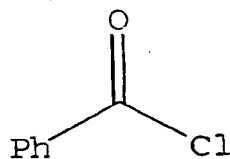
- (c) reacting the compound formed in step (b) with a compound having the structure:



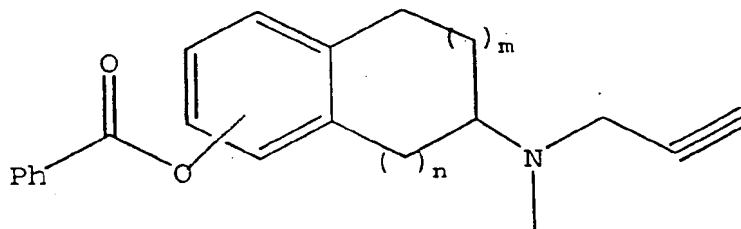
wherein X is a leaving group;  
to form a compound having the structure:



- (d) reacting the compound formed in step (c) with a compound having the structure:



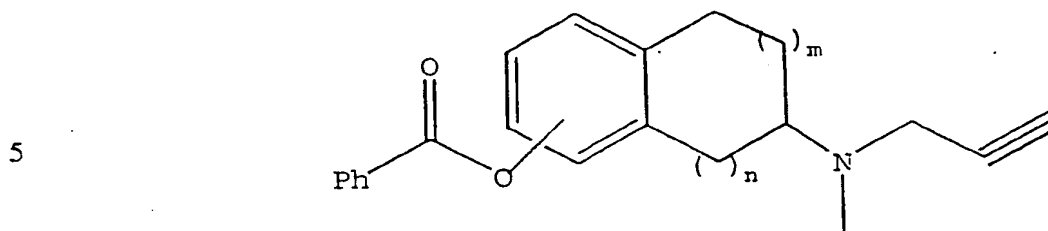
in the presence of 4-dimethylaminopyridine (DMAP) and an aprotic solvent to form a compound having the structure:



In one embodiment, the aprotic solvent in step (c) is  $\text{CHCl}_3$ .

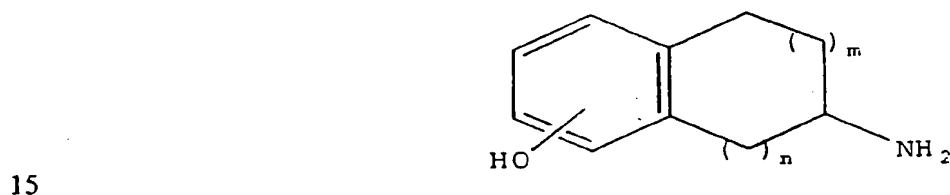
-60-

The subject invention provides yet another process for preparing a compound having the structure:

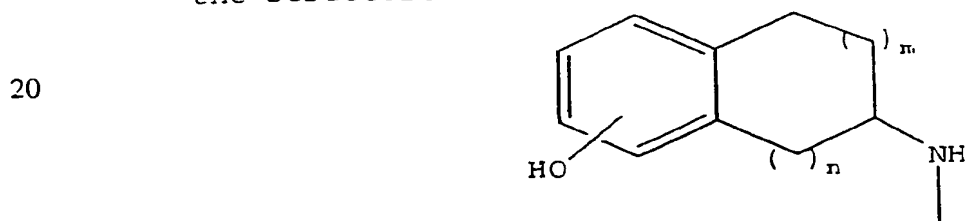


which comprises:

- 10 (a) reacting a compound having the structure:



with NaCNBH<sub>3</sub>/paraformaldehyde to produce a compound having the structure:

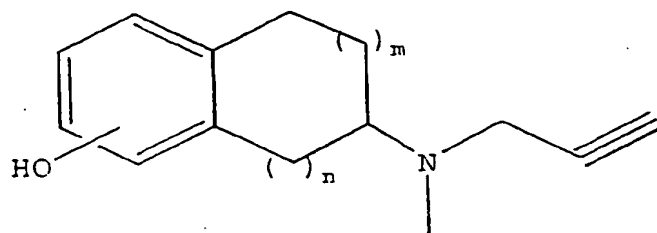


- 25 (b) reacting the compound formed in step (a) with a compound having the structure:



wherein X is a leaving group,  
to form a compound having the structure:

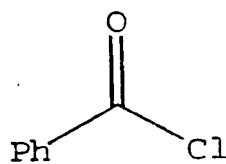
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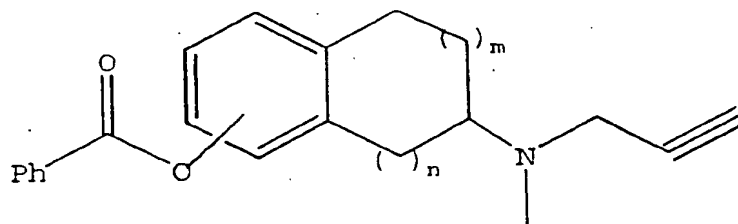
(c) reacting the compound formed in step (b) with a compound having the structure:

10



in the presence of 4-dimethylaminopyridine (DMAP) and an aprotic solvent to form a compound having the structure:

15

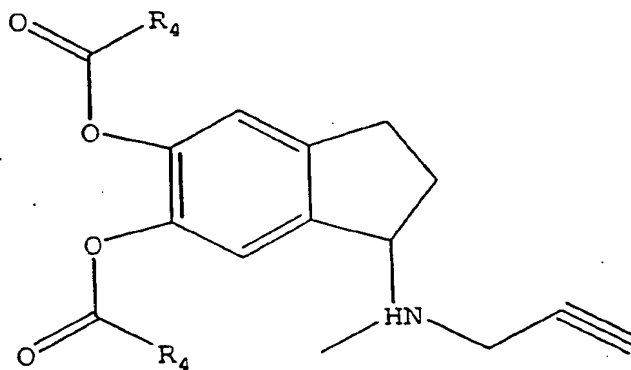


20

In one embodiment, the aprotic solvent in step (d) is CHCl<sub>3</sub>.

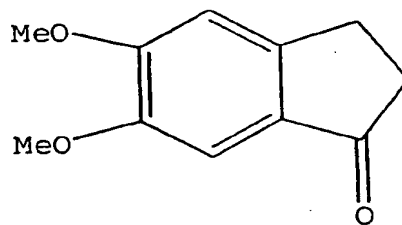
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The subject invention further provides a process for preparing a compound having the structure:

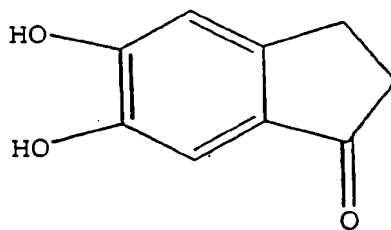


which comprises:

(a) reacting a compound having the structure:

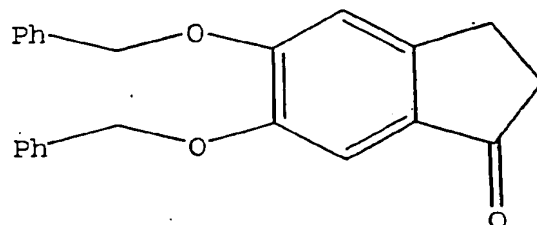


with  $AlCl_3$ , or  $BBr_3$ , in the presence of toluene to produce a compound having the structure:

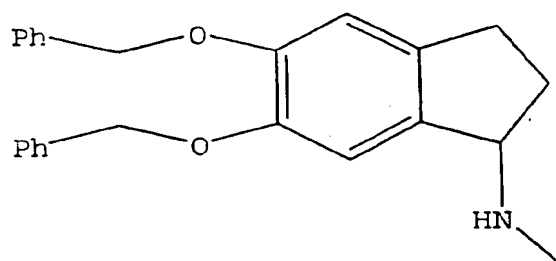


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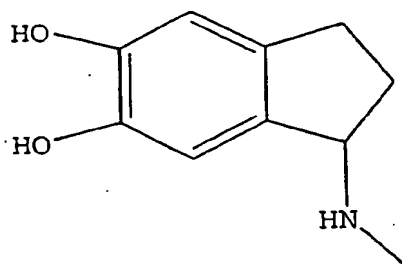
- (b) reacting the product formed in step (a) with benzyl chloride and  $K_2CO_3$  in the presence of dimethyl formamide (DMF) to produce a compound having the structure:



- 10 (c) reacting the product formed in step (b) with  $MeNH_2 \cdot HCl$ ,  $NaCNBH_3$  in tetrahydrofuran (THF)/MeOH to produce a compound having the structure:

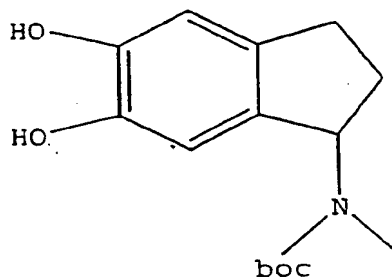


- 20 (d) reacting the product formed in step (c) with  $H_2$ , Pd/C and MeOH to produce a compound having the structure:

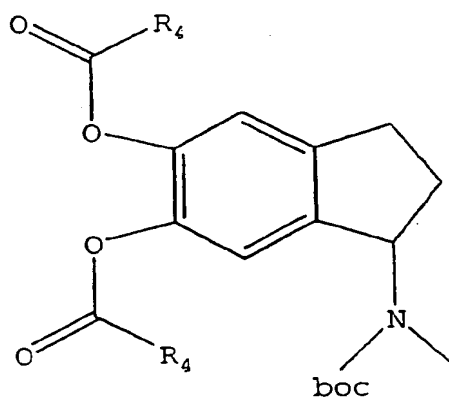


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- (e) reacting the product formed in step (d) with  $\text{Boc}_2\text{O}$ , dioxane/ $\text{H}_2\text{O}$  and  $\text{NaHCO}_3$  to produce a compound having the structure:

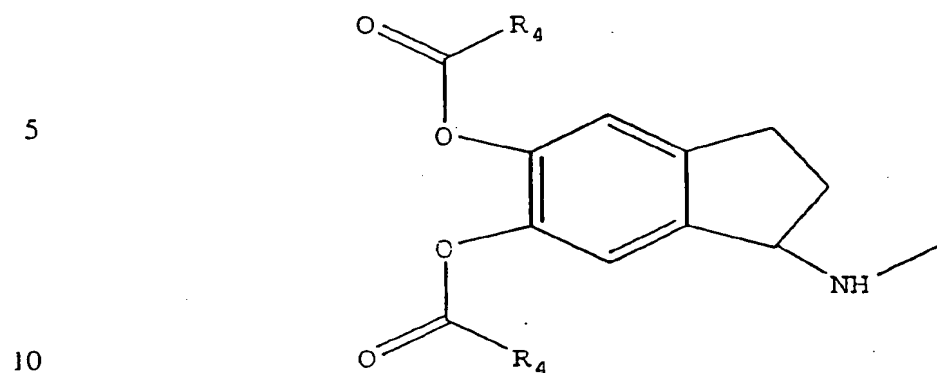


- (f) reacting the product formed in step (e) with  $\text{R}_4\text{COCl}$ ,  $\text{Et}_3\text{N}$  in  $\text{CH}_2\text{Cl}_2$  in the presence of 4-dimethylaminopyridine (DMAP) to produce a compound having the structure:

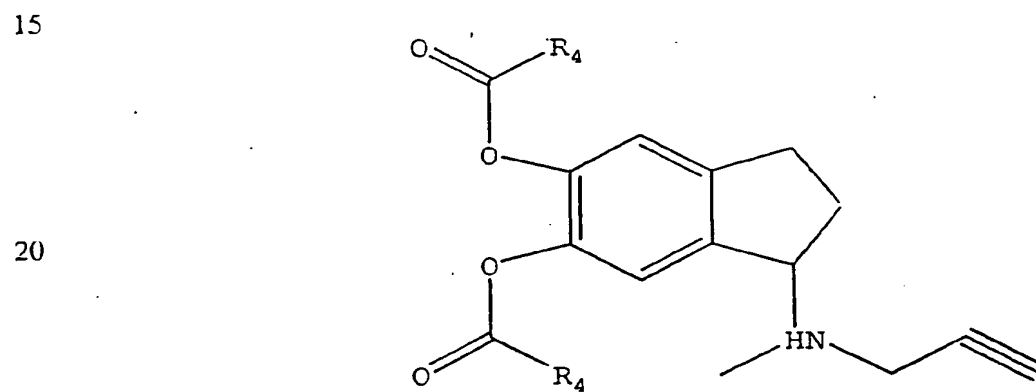


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- (g) reacting the product formed in step (f) with HCl/dioxane to produce a compound having the structure:

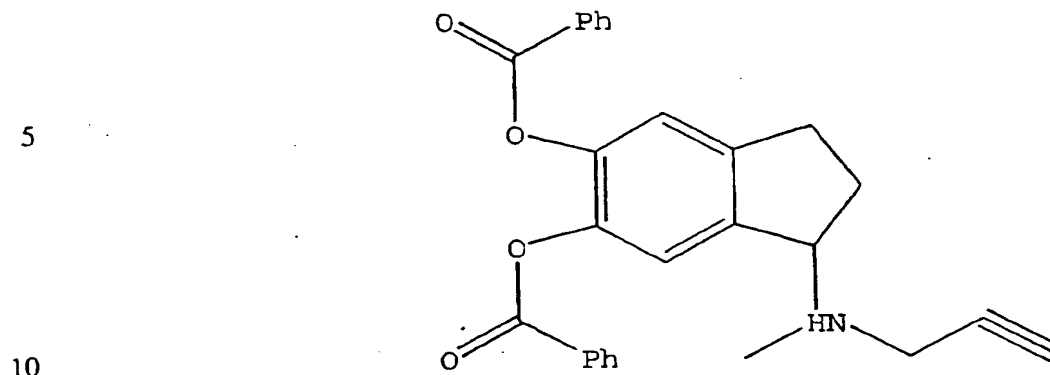


- (h) reacting the product formed in step (g) with propargyl bromide,  $K_2CO_3$  in  $CH_3CN$  and then with HCl/ether and MeOH to produce a compound having the structure:



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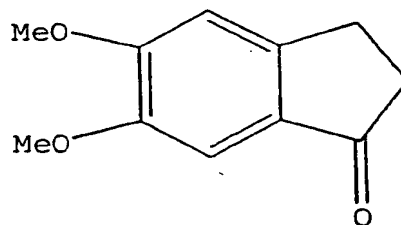
Also, the subject invention provides a process for preparing a compound having the structure:



which comprises:

(a) reacting a compound having the structure:

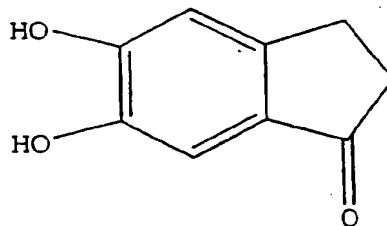
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with  $\text{AlCl}_3$  or  $\text{BBR}_3$  in the presence of toluene to produce a compound having the structure:

25

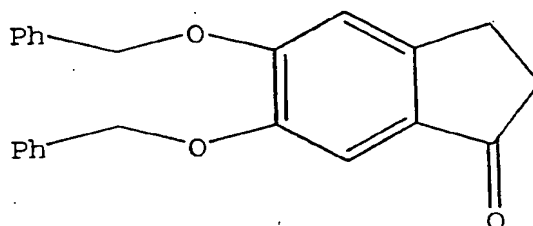


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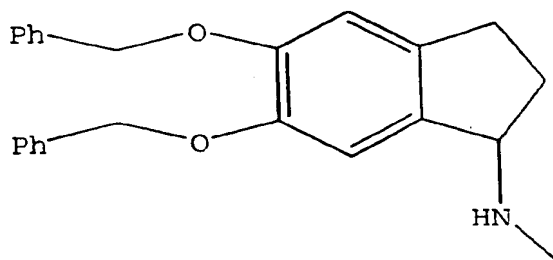
- (b) reacting the product formed in step (a) with benzyl chloride and  $K_2CO_3$  in the presence of dimethyl formamide (DMF) to produce a compound having the structure: .

5



- 10 (c) reacting the product formed in step (b) with  $MeNH_2 \cdot HCl$ ,  $NaCNBH_3$  in tetrahydrofuran (THF)/MeOH to produce a compound having the structure:

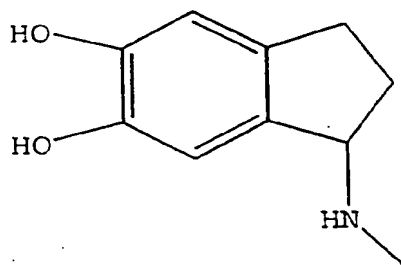
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20

- (d) reacting the product formed in step (c) with  $H_2$ , Pd/C and MeOH to produce a compound having the structure:

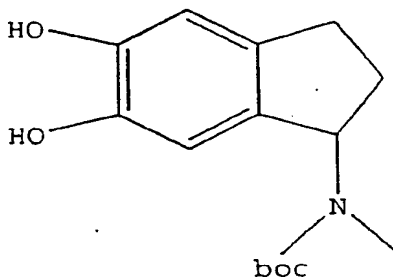
25



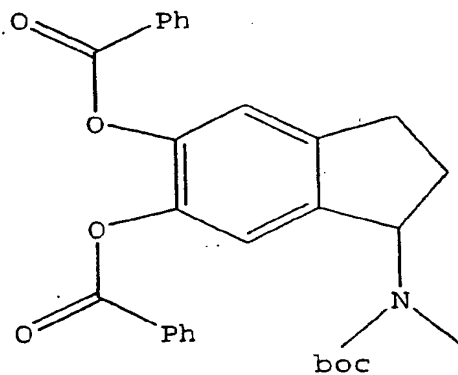
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- (e) reacting the product formed in step (d) with  $\text{Boc}_2\text{O}$ , dioxane/ $\text{H}_2\text{O}$  and  $\text{NaHCO}_3$  to produce a compound having the structure:

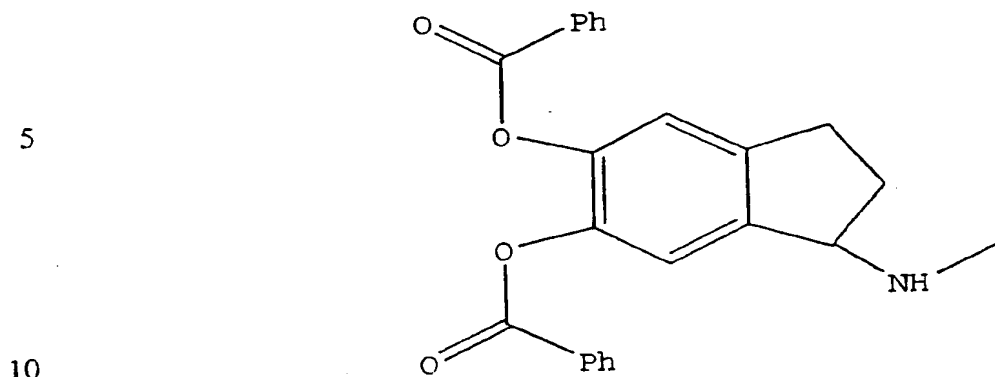


- 10
- (f) reacting the product formed in step (e) with  $\text{PhCOCl}$ ,  $\text{Et}_3\text{N}$  in  $\text{CH}_2\text{Cl}_2$ , in the presence of 4-dimethylaminopyridine (DMAP) to produce a compound having the structure:

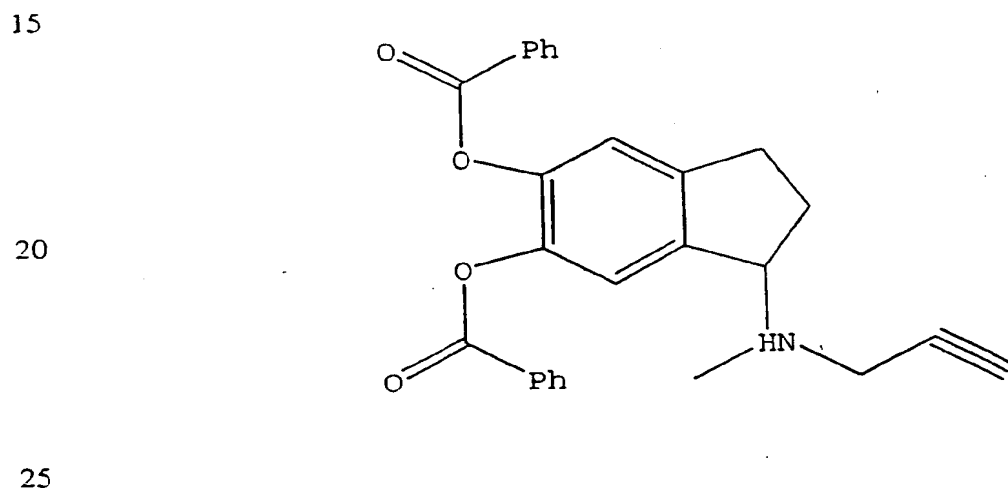


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- (g) reacting the product formed in step (f) with HCl/dioxane to produce a compound having the structure:

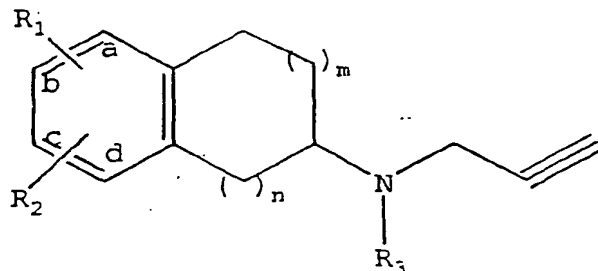


- (h) reacting the product formed in step (g) with propargyl bromide, K<sub>2</sub>CO<sub>3</sub> in CH<sub>3</sub>CN and then with HCl/ether and MeOH to produce a compound having the structure:



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The subject invention further provides the use of a compound or a prodrug of a compound which becomes the compound having the structure:



wherein  $R_1$  is OH or  $OC(O)R_4$ ;

wherein  $R_2$  is H, OH or  $OC(O)R_4$ ,

wherein  $R_4$  is branched or unbranched  $C_1$  to  $C_6$  alkyl, aryl, aralkyl or  $NR_5R_6$ ,

wherein  $R_5$  and  $R_6$  are each independently H,  $C_1$  to  $C_8$  alkyl,  $C_6$  to  $C_{12}$  aryl,  $C_6$  to  $C_{12}$  aralkyl or  $C_6$  to  $C_{12}$  cycloalkyl, each optionally substituted;

wherein  $R_3$  is H or  $C_1$  to  $C_6$  alkyl;

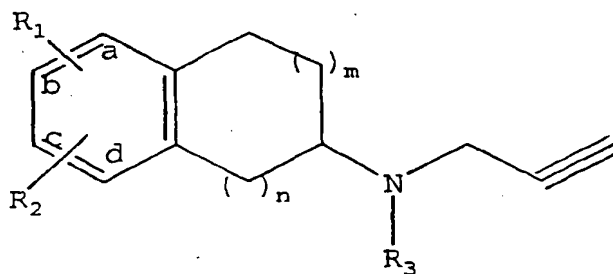
wherein  $n$  is 0 or 1; and

wherein  $m$  is 1 or 2,

or a pharmaceutically acceptable salt thereof,

for the manufacture of a medicament for treating a subject afflicted with a neurological disease, wherein the compound is to be periodically administered to the subject in a therapeutically effective dose.

The subject invention also provides the use of a compound or a prodrug of a compound which becomes the compound having the structure:



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wherein  $R_1$  is OH or  $OC(O)R_9$ , and

wherein  $R_9$  is branched or unbranched  $C_1$  to  $C_6$  alkyl, aryl, or aralkyl;

$R_2$  is H or  $OC(O)R_4$ , or both  $R_1$  and  $R_2$  are  $OC(O)R_4$ ,

wherein  $R_4$  is branched or unbranched  $C_1$  to  $C_6$  alkyl, aryl, aralkyl or  $NR_5R_6$ ,

wherein  $R_5$  and  $R_6$  are each independently H,  $C_1$  to  $C_8$  alkyl,  $C_6$  to  $C_{12}$  aryl,  $C_6$  to  $C_{12}$  aralkyl or  $C_6$  to  $C_{12}$  cycloalkyl, each optionally substituted;

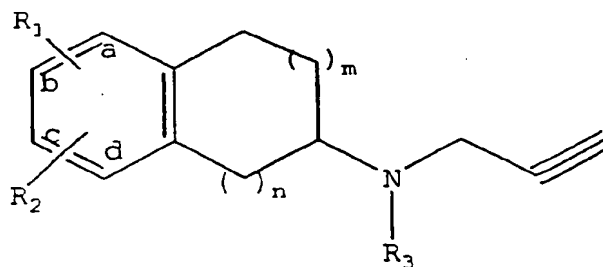
wherein  $R_3$  is H or  $C_1$  to  $C_6$  alkyl;

wherein  $n$  is 0 or 1; and

wherein  $m$  is 1 or 2,

or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating neurological disease in a subject, wherein the compound is to be periodically administered to the subject in a therapeutically effective dose.

In one embodiment of the use, the compound has the structure:



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wherein  $R_1$  is  $OC(O)R_9$  and  $R_2$  is H,

wherein  $R_9$  is branched or unbranched  $C_1$  to  $C_6$  alkyl, aryl, or aralkyl, or

$R_1$  is  $OC(O)R_4$  and  $R_2$  is  $OC(O)R_4$ ,

wherein  $R_4$  is branched or unbranched  $C_1$  to  $C_6$  alkyl, aryl, aralkyl or  $NR_5R_6$ ,

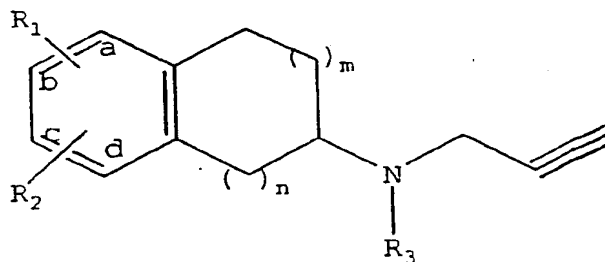
wherein  $R_5$  and  $R_6$  are each independently H,  $C_1$  to  $C_6$  alkyl,  $C_6$  to  $C_{12}$  aryl,  $C_6$  to  $C_{12}$  aralkyl or  $C_6$  to  $C_{12}$  cycloalkyl, each optionally substituted;

wherein  $R_3$  is H or  $C_1$  to  $C_6$  alkyl;

wherein  $n$  is 0 or 1; and

wherein  $m$  is 1 or 2.

In another embodiment of the use, the compound has the structure:



wherein  $R_1$  is OH;

wherein  $R_2$  is H or  $OC(O)R_4$  when  $R_1$  is attached to the "a" carbon or the "d" carbon, or

$R_2$  is  $OC(O)R_4$  when  $R_1$  is attached to the "b" carbon or the "c" carbon;

wherein  $R_4$  is  $C_1$  to  $C_6$  branched or unbranched alkyl, aryl, aralkyl or  $NR_5R_6$ ,

wherein  $R_5$  and  $R_6$  are each independently H,  $C_1$  to  $C_6$  alkyl,  $C_6$  to  $C_{12}$  aryl,  $C_6$  to  $C_{12}$  aralkyl or  $C_6$  to  $C_{12}$  cycloalkyl, each optionally substituted;

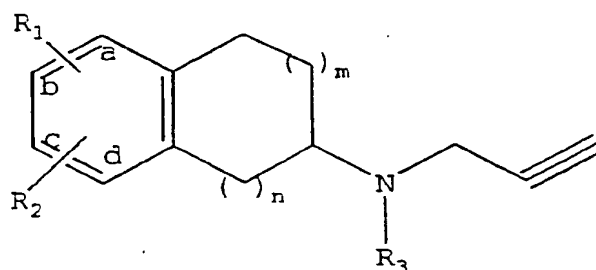
wherein  $R_3$  is H or  $C_1$  to  $C_6$  alkyl;

wherein  $n$  is 0 or 1; and

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wherein m is 1 or 2.

In an additional embodiment of the use, the compound has the structure:



wherein the compound is an optically pure enantiomer;  
wherein R<sub>1</sub> is OH;  
wherein R<sub>2</sub> is H;  
wherein R<sub>3</sub> is H or C<sub>1</sub> to C<sub>6</sub> alkyl;  
wherein n is 0 or 1; and  
wherein m is 1 or 2.

In a further embodiment of the use, the subject is human.

In yet another embodiment of the use, the medicament is formulated for oral, parenteral, intravenous, transdermal, or rectal administration.

In an embodiment of the use, the therapeutically effective amount is from about 0.01 mg per day to about 50.0 mg per day.

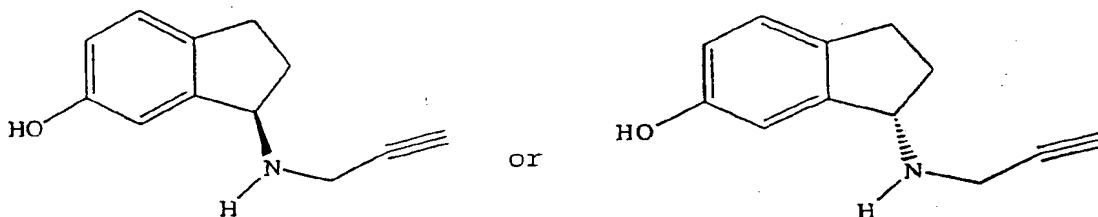
In an added embodiment of the use, the therapeutically effective amount is from about 0.1 mg per day to about 100.0 mg per day.

In still another embodiment of the use, the therapeutically effective amount is from about 0.1 mg per day to about 10.0 mg per day.

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In an embodiment of the use, the neurological disease is Parkinson's disease, Alzheimer's disease, depression, epilepsy, narcolepsy, amyotrophic lateral sclerosis (ALS), memory disorders, panic, post-traumatic stress disorder (PTSD), sexual dysfunction, attention deficit and hyperactivity syndrome (ADHD), attention deficit disorder, or Tourette's syndrome.

In a further embodiment of the use, the neurological disease is depression. In one embodiment, the compound has the structure:



The subject invention thus discloses various derivatives and isomers of hydroxylated propargylamino indan and tetralin which have surprisingly varied potency and selectivity for MAO inhibition. The subject invention also provides modifications of the hydroxy compounds which have surprisingly varied MAO inhibitory properties depending upon the substitution pattern, however, the hydroxy compound is always a more potent inhibitor than the modified version. Thus, the modified version may be considered a prodrug of the more active hydroxy compound into which it will be metabolized in vivo.

In one embodiment of the invention, the prodrug compound is a carboxylic acid ester of the hydroxy compound. In another embodiment, the parent is a carbamate derivative of the hydroxy compound.

As discussed above, carbamate propargylamino indans and

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tetralins have been reported in PCT International Application No. PCT/US97/24155 as both MAO inhibitors and AchE inhibitors. However, it is a further embodiment of this invention that such a prodrug compound will not be a potent inhibitor of AchE ( $IC_{50} > 500$  micromolar), and the  $IC_{50}$  for MAO-A inhibition of the  
5 corresponding hydroxy metabolite be at least 100 times more potent than the prodrug.

In one embodiment, the compounds are dihydroxy derivatives of propargylamino indan or tetralin. These derivatives are  
10 expected to be antioxidants, as well as MAO inhibitors. In another embodiment, the subject invention provides ester prodrugs.

Thus, the subject invention provides esters or carbamates of  
15 propargylamino indanols, propargylamino indandiols, propargylamino tetralinols or propargylamino tetralindiols, and may be prepared by methods of esterification or carbamoylation of hydroxy compounds. Ester derivatives (Figure 1) when  $R_2$  equals hydrogen were prepared by reacting the propargylamino  
20 indanols with acyl chlorides in the presence of a strong organic acid such as trifluoroacetic acid or an acylation catalyst such as 4-dimethylaminopyridine (DMAP), with or without an inert organic solvent such as chloroform. Compounds when  $R_3$  equals hydrogen were prepared either by direct acylation as described  
25 above, or by first N-protecting the amine moiety, e.g., by a tert-butoxycarbonyl (Boc) group, followed by acylation as above, and finally removing the protecting group. The preparation of compounds of the subject invention which are carbamates is described in PCT/US97/24155.

30

Propargylamino indanols may be prepared by reacting amino indanols with propargyl bromide in a polar organic solvent such as N,N-dimethylacetamide or acetonitrile in the presence of a base such as potassium carbonate. N-Methyl, N-propargylamino

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indanols may be prepared by reductive alkylation of propargylamino indanols by methods known to those skilled in the art, e.g., with  $\text{NaCNBH}_3$  and paraformaldehyde. Alternatively, N-methyl,N-propargylamino indanols were prepared by first methylating amino indanols either by  $\text{NaCNBH}_3$ /paraformaldehyde or by ethyl formate followed by  $\text{LiAlH}_4$  reduction, and then reacting the N-methylamino indanols thus obtained with propargyl bromide as described above.

The N-propargyl derivatives of, *inter alia*, 3-amino-indan-4-ol, 1-amino-indan-4-ol, 3-amino-indan-5-ol and 7-amino-5,6,7,8-tetrahydro-naphthalen-2-ol were prepared.

Compounds of the subject invention with both  $\text{R}_1$  and  $\text{R}_2$  equal to  $\text{OCOR}_4$  (see Figure 2, compound numbered 9) were prepared by propargylation of 5,6-di-O-benzoyl-1-methylamino-1-indan (Figure 2, compound numbered 8), as described above. 5,6-Di-O-benzoyl-1-methylamino-1-indan (Figure 2, compound numbered 8) was prepared from 5,6-bis-benzyloxy-1-indanone 3 as follows:

- 1) reductive amination of the compound numbered 3 in Figure 2 as described above gave 5,6-bis-benzyloxy-1-indanyl)methylamine (Figure 2, compound numbered 4);
- 2) the compound numbered 4 in Figure 2 was debenzylated by catalytic hydrogenation and protected by the Boc group to give N-Boc-1-methylamino-indan-5,6-diol (Figure 2, compound numbered 6); and
- 3) Compound 6 in Figure 2 was esterified as described above and the protecting group removed as previously described to give 5,6-di-O-benzoyl-1-methylamino-1-indan (Figure 2, compound numbered 8).

The diester tetralin derivative numbered 12 (Figure 3) was prepared by esterification of the dihydroxy tetralin numbered 11 (Figure 3).

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Table 1. Chemical Data

compd #	ster	R <sub>2</sub>	R <sub>1</sub>	R <sub>1</sub> pos	R <sub>3</sub>	n	m	mp	formula	yield (%)
100*	S	H	OH	6	H	0	1	175-7	C <sub>13</sub> H <sub>17</sub> NO <sub>4</sub> S	45
101*	R	H	OH	6	H	0	1	173-5	C <sub>13</sub> H <sub>17</sub> NO <sub>4</sub> S	42
102	S	H	OCOMe	6	H	0	1	138-40	C <sub>14</sub> H <sub>16</sub> ClNO <sub>2</sub>	46
103	R	H	OCOMe	6	H	0	1	156-8	C <sub>14</sub> H <sub>16</sub> ClNO <sub>2</sub>	77
104	S	H	OCOtBu	6	H	0	1	126-8	C <sub>17</sub> H <sub>22</sub> ClNO <sub>2</sub>	67
105	R	H	OCOtBu	6	H	0	1	128-30	C <sub>17</sub> H <sub>22</sub> ClNO <sub>2</sub>	46
106	S	H	OCOnBu	6	H	0	1	149-50	C <sub>17</sub> H <sub>22</sub> ClNO <sub>2</sub>	37
107	R	H	OCOnBu	6	H	0	1	155-7	C <sub>17</sub> H <sub>22</sub> ClNO <sub>2</sub>	85
108	S	H	OCOCH <sub>2</sub> Ph	6	H	0	1	144-5	C <sub>20</sub> H <sub>20</sub> ClNO <sub>2</sub>	22
109	R	H	OCOCH <sub>2</sub> Ph	6	H	0	1	145-7	C <sub>20</sub> H <sub>20</sub> ClNO <sub>2</sub>	52
110	S	H	OCOPh	6	H	0	1	202-4	C <sub>19</sub> H <sub>18</sub> ClNO <sub>2</sub>	18
111	R	H	OCOPh	6	H	0	1	210-11	C <sub>19</sub> H <sub>18</sub> ClNO <sub>2</sub>	61
112	rac	H	OH	6	Me	0	1	210-11	C <sub>13</sub> H <sub>16</sub> ClNO	70
113	S	H	OH	6	Me	0	1	82-4	C <sub>13</sub> H <sub>16</sub> ClNO	72
114	R	H	OH	6	Me	0	1	71-2	C <sub>13</sub> H <sub>16</sub> ClNO	78
115	S	H	OCOMe	6	Me	0	1	168-70	C <sub>15</sub> H <sub>18</sub> ClNO <sub>2</sub>	95
116	R	H	OCOMe	6	Me	0	1	168-70	C <sub>15</sub> H <sub>18</sub> ClNO <sub>2</sub>	93
117	rac	H	OH	4	Me	0	1	160-62	C <sub>13</sub> H <sub>16</sub> NCIO	89
118	rac	H	OH	7	Me	0	1	83-5	C <sub>13</sub> H <sub>16</sub> NCIO	53
119	rac	H	OCOMe	4	Me	0	1	148-50	C <sub>15</sub> H <sub>18</sub> ClNO <sub>2</sub>	72
120	rac	H	OCOPh	4	Me	0	1	176-8	C <sub>20</sub> H <sub>20</sub> ClNO <sub>2</sub>	59
121	rac	H	OCOPh(OMe) <sub>2</sub>	4	Me	0	1	183-5	C <sub>22</sub> H <sub>24</sub> ClNO <sub>4</sub>	39
122	rac	H	OCOPh	7	Me	0	1	185-7	C <sub>20</sub> H <sub>20</sub> ClNO <sub>2</sub>	45
123	rac	H	OH	7	Me	1	1	220-1	C <sub>14</sub> H <sub>18</sub> NCIO	66
124	rac	H	OCOPh	7	Me	1	1	104-6	C <sub>21</sub> H <sub>22</sub> ClNO <sub>2</sub>	71
125	S	H	OCOnBu	6	Me	0	1	78-80	C <sub>18</sub> H <sub>24</sub> ClNO <sub>2</sub>	73
126	R	H	OCOnBu	6	Me	0	1	96-8	C <sub>18</sub> H <sub>24</sub> ClNO <sub>2</sub>	72
127	S	H	OCOPh	6	Me	0	1	73-5	C <sub>20</sub> H <sub>20</sub> ClNO <sub>2</sub>	52
128	R	H	OCOPh	6	Me	0	1	82-4	C <sub>20</sub> H <sub>20</sub> ClNO <sub>2</sub>	56

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Table 1. Chemical Data cont.

129	S	H	OCOtBu	6	Me	0	1	153-5	C <sub>18</sub> H <sub>24</sub> ClNO <sub>2</sub>	73
130	R	H	OCOtBu	6	Me	0	1	155-7	C <sub>18</sub> H <sub>24</sub> ClNO <sub>2</sub>	78
131	S	H	OCOPh(Me)	6	Me	0	1	**	C <sub>21</sub> H <sub>22</sub> ClNO <sub>2</sub>	51
132	R	H	OCOPh(Me)	6	Me	0	1	82-4	C <sub>21</sub> H <sub>22</sub> ClNO <sub>2</sub>	46
133	S	H	OCOPh(OMe) <sub>2</sub>	6	Me	0	1	118-20	C <sub>22</sub> H <sub>24</sub> ClNO <sub>2</sub>	58
134	R	H	OCOPh(OMe) <sub>2</sub>	6	Me	0	1	73-5	C <sub>22</sub> H <sub>24</sub> ClNO <sub>2</sub>	68
135	rac	H	OH	7	H	0	1	166-8	C <sub>12</sub> H <sub>14</sub> ClNO	35
136	rac	H	OH	4	H	0	1	196-8	C <sub>12</sub> H <sub>14</sub> ClNO	66
137	rac	OCOPh (5-pos)	OCOPh	6	Me	0	1	114-5	C <sub>27</sub> H <sub>24</sub> ClNO <sub>4</sub>	59
138	rac	OCOPh (6-pos)	OCOPh	7	Me	1	1	180-2	C <sub>28</sub> H <sub>26</sub> ClNO <sub>4</sub>	58

ster = stereochemistry

pos = position

mesylate salts

\*\* wide range, hygroscopic

Table 2.  $^1\text{H}$ -NMR Data ( $R_1 = R_2 = \text{H}$ ) (300 MHz, dimethyl sulfoxide ( $\text{DMSO}$ )- $d_6$ )

DMSO) - d <sub>6</sub> )								
Cmpd #	Ph	indan			Pg		R <sub>4</sub>	NH <sub>2</sub>
		C3-H	C2-H	C1-H	CH <sub>2</sub>	CH		
102	7.52(d)	4.79(m)	2.43(m)	2.83(m)	3.88(m)	3.71(m)	2.27 (Me,s)	10.2 (br s)
103	7.35(d) 7.10(dd)							
104	7.48(d)	4.79(m)	2.45(m)	2.85(m)	3.90(m)	3.72(m)	1.30 (tBu,s)	10.15 (br s)
105	7.36(d) 7.07(dd)							
108	7.48(d)	4.80(m)	2.45(m)	2.85(m)	3.91(m)	3.72(m)	7.38(m,1H)	10.2 (br s)
109	7.36(d) 7.07(dd)						7.33(m,4H)  3.99(CH <sub>2</sub> ,s)	
106	7.48(d)	4.79(m)	2.45(m)	2.85(m)	3.90(m)	3.71(m)	2.57(t,2H)	10.1 (br s)
107	7.55(d) 7.08(dd)						1.61(m,2H) 1.38(m,2H) 0.91(t,3H)	
110	7.67(d)	4.83(m)	2.46(m)	2.86(m)	3.93(m)	3.72(m)	8.13(d,2H)	10.15 (d)
111	7.42(d) 7.28(dd)						7.76(t,1H) 7.61(t,2H)	

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Table 3.  $^1\text{H}$ -NMR Data ( $R_1 = \text{H}$ ,  $R_2 = \text{Me}$ ) (300 MHz,  $\text{D}_2\text{O}$ )

Cmpd #	Ph	Indan			Propargyl		$R_4$	N-Me
		C3-H	C2-H	C1-H	$\text{CH}_2$	CH		
5	116	7.50(d)						
		7.35(d)	5.22(m)	2.46(m)	3.07(m)	4.05(m)	3.15(m)	2.37(Me,s)
	115	7.25(dd)		2.60(m)	3.17(m)			2.83(s)
	126	7.50(d)					2.69(t,2H)	
		7.33(d)	5.23(m)	2.49(m)	3.07(m)	4.05(m)	3.17(m)	1.73(m,2H)
	125	7.22(dd)		2.62(m)	3.17(m)			1.44(m,2H)
10							0.97(t,3H)	
	128	7.50(d)					8.11(dd,2H)	
		7.40(d)	5.17(m)	2.57(m)	3.06(m)	4.00(m)	3.15(m)	7.74(dt,1H)
15	127	7.29(dd)		2.47(m)	3.17(m)			7.57(t,2H)
	129	7.49(d)						
		7.28(d)	5.20(m)	2.60(m)	3.05(m)	4.03(m)	3.17(m)	1.37(s,9H)
	130	7.21(dd)		2.45(m)	3.16(m)			2.81(s)
	131	7.90(d,1H)						
		7.44(t,1H)	5.02(m)	2.50(m)	3.08(m)	3.93(m)	3.14(m)	For Ar H's, see under Ph.
20	132	7.36(m,2H)		2.40(m)	2.95(m)			2.43(s,Me)
		7.21(m,2H)						
		7.08 (dd,1H)						
	133	7.5-7.1						
		(m,4H)	5.05 (br d)	2.50(m)	3.08(m)	3.92(m)	3.16(m)	For Ar H's, see under Ph.
	134	6.74(dd,2H)		2.41(m)	2.95(m)			3.84 (s,6H, OMe)

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